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BULLETIN

OF

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THE JOHNS HOPKINS PRESS

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PERLÈCHE

A Consideration of Its Etiology and Pathology

M. H. GOODMAN, A.B., M.D.

From the Johns Hopkins Medical School, Department of Dermatology

Perlèche is a disease more commonly occurring in infants and children but is also quite often seen in adults. It affects the skin and mucous membrane of the commissures of the lips, causing inflammation with maceration, thickening and desquamation of the epidermis. Sometimes fissures form that may be painful and bleed when the mouth is opened widely. The disease runs a course of a few weeks or longer but has a great tendency to relapse and may become chronic, especially in adults. Among children it is contagious and epidemics have occurred in institutions. As may be seen in the accompanying table, a number of different organisms have been incriminated as being responsible for the condition. At first various cocci were held to play the principal rôle in the causation of the disease but in the last few years a number of investigators have cultivated chiefly yeast-like organisms from the lesions.

It is an established fact that yeast-like fungi of the monilia group and closely related types can occur as saprophytes on normal skin. Bloch (1) obtained positive cultures of oïdium, monilia, yeast and pityrosporon in 81 per cent of 59 cases which included normal subjects as well as others suffering from various skin affections. Jessner and Kleiner (2) isolated fungi from the nail groove in about 60 per cent of normal persons. They also showed that one can produce clinical pictures similar in many instances to those described for some of the superficial mycotic infections by inoculating the normal skin with fungi, provided there has been a previous maceration and scarification. Dowling (3) found that species of monilia cultivated from the skin exhibited feeble virulence in experiments on laboratory animals. He concluded that these fungi are aroused from their

saprophytic existence only with difficulty, ideal conditions such as hyperidrosis, wet occupations, continuous water-bath therapy, etc., *being necessary* for their active proliferation. Greenbaum and Klauder (4), in a study of the saccharomycetic flora of the normal skin in 150 cases, cultured yeasts which they separated into four different types on the basis of morphologic, biologic and cultural differences. These observers obtained from seven cases of interdigital disease of the hands cultures of three types of yeasts which corresponded to the first three types obtained in the normal flora. Shelmire (5) stressed the importance of the direct examination of particles

TABLE 1

Different types of organisms isolated in cases of perlèche by various investigators

AUTHOR	DATE	ORGANISMS FOUND IN LESIONS
Lemaistre	1885	Streptococcus plicatilis (anaërobic)
Raymond	1895	Staphylococcus cereus albus
Planche	1897	Staphylococcus pyogenes aureus and albus
Sabouraud	1906	Streptococcus
Smith	1917	In early stage—Anaërobic streptococcus In late stage—Staphylococcus
Lane	1917	Streptococcus
Finnerud	1929	Monilia and cryptococcus
Skolnik	1930	Cryptococcus
Macleod	1930	Monilia
Schwab	1931	Streptococcus; staphylococcus; diplococcus
Hopkins	1932	Monilia albicans
Robinson and Moss	1932	Monilia albicans

of epidermis in order to determine the presence of hyphal forms as the causative agents in certain eczema-like and intertriginous eruptions, including the so-called "erosio interdigitalis blastomycetica" of Fabry. He attributed the frequent association of this latter condition with yeasts to the fact that most investigators have made only smears and cultures from the lesions and, therefore, have missed the mycelia and spores of oïdium albicans, the organism which he blamed for most of these eruptions. From these observations, we must assume that if, for example, in the erosio interdigitalis we are dealing with a mycotic infection, then either an oïdium or a simple, pure, yeast-like organism is responsible, and one or the other is a secondary

invader, or on the other hand, the two types are jointly the provoking agents.

With regard to the superficial yeast infections, as with the superficial fungus infections in general, it may be said that much confusion still exists as to the specificity of the various types of organisms in producing any particular local disease of the skin or mucous membrane. It is a fact, however, that the yeast-like organisms are found in sufficient numbers in certain inflammatory conditions to convince us that they can either provoke or at least maintain in an active state, by their multiplication, these diseases, which it is safe to assume may have as their primary cause a peculiar vulnerability of the intertriginous areas because of the presence of moisture, heat or certain bacterial agents.

In 1929 Finnerud (6) reported an epidemic of perlèche in an orphanage near Chicago in which 100 cases occurred. In 77 per cent of these cases fungi of the monilia or cryptococcus type were isolated. Much skepticism was expressed at the time by those who discussed the author's report, most of them contending that no provision was made in his study for cultivating the streptococcus or staphylococcus, which had until then been held to be the primary provoking agents of the disease (7). Finnerud reproduced the affection, however, and it would seem from his studies that the yeast-like organisms can, under certain conditions, produce a typical perlèche, or at least participate, if only as a secondary invader, in producing the pathology of this disease. In a series of cases in which lesions of the perlèche type occurred in association with buccal moniliasis, Macleod (8) found monilias microscopically and culturally, while streptococci and staphylococci were absent. Skolnik (9) recently studied five cases of chronic bilateral perlèche in adults. He cultured cryptococci from all the cases and found that control cultures made from the angles of normal mouths revealed only bacteria.

The observations above serve to indicate the confusion still existing in the matter of the exact etiology of the superficial yeast infections and particularly with respect to the subject of perlèche. Because of this fact it was considered pertinent to add to the literature certain studies made on a case of chronic perlèche in an adult, especially since the patient permitted biopsies which permitted a microscopical

examination of the entire lesion at each angle of the mouth. Only one report on the histology of this disease appears in the literature, that by Auché (10) in 1906, based on a single case in a child six years of age. He stated that the dermic tissue in his preparations was represented simply by two or three hypertrophied and elongated papillae which occupied the center of the section and that the deeper tissue was not present in the section.

CASE REPORT

Case 1. I. H., a Jewess, aged 56, was first seen in the Clinic for the conditions in question on June 13, 1931. She complained of an itching sensation in the third interspace of the right hand and some soreness at the angles of the mouth when she opened it widely. The disorder in the web of the finger, so far as she could recall, had been present for more than ten years, but it did not bother her when she kept it dry. She claimed that the sore which was present at each angle of the mouth had been there for about ten years and insisted that they came on after the lesion in the web of the hand had already been present for a time (figs. 1 and 2).

On the third web of the right hand there was the typical picture of the so-called erosio interdigitalis blastomycetica, the central dull red area of erosion with the encircling collarette of uplifted, but clinging, thick, whitish, soggy scale. There was a slight exaggeration of the normal fold at both angles of the mouth, produced by a drooping of the upper lip. On the left commissure, directly over the vermilion, there was a pearly, bead-like, soft, whitish, match-head-sized papule. This papule bridged a fissure which extended outward from it for a short distance into the adjacent skin and inward into the mucous membrane of the lip. Above and below, the papule was flanked by a fissure, each of which was covered with a thin crust. The skin and mucous membrane adjacent to the fissures were slightly thickened, reddish and scaly. On the right commissure there was a lesion similar in every respect to that on the left, but apparently not quite as advanced or as active.

This patient presented also a disease of the nail of the third finger of the right hand (fig. 2). The outer portion of the nail-plate showed longitudinal grooves and ridges with marked thickening, opacity and blackish-grey discoloration. Inoculation of scrapings from this nail in Sabouraud's maltose agar yielded a profuse growth of an organism (fig. 3), which on microscopic examination appeared as short, rod-like, slightly branching mycelia with numerous spores. The identity of this organism was not established, since the disease of the nail was not considered of special interest to the purpose of this paper.

The general examination of the patient was of no significance with respect to the disease of the skin. The blood Wassermann was negative. The urine was negative for sugar and albumin. There was no clinical ringworm infection, except possibly that of the nail, but a trichophytin test was strongly positive.

Cultural and morphologic observations. Scrapings were made from the lesion at the left angle of the mouth and also from the interdigital lesion. These were placed in potassium hydrate solution and examined directly. A number of

FIG. 1. CHRONIC BILATERAL PERLÈCHE

Note the small papule in the center of the erosive lesion on the left commissure of the lips.

FIG. 2. EROSIO INTERDIGITALIS BLASTOMYCETICA THIRD WEB, IN THE CASE OF CHRONIC PERLÈCHE

Note also the changes in the nail of the third finger

mycelial threads were seen in each specimen but no spores were noted. The threads appeared to be similar in the two specimens, but details were not noted at the time. Cultures made on Sabouraud's maltose agar in three to five days showed small, elevated, whitish colonies which then gradually coalesced to form a

pasty, whitish, smooth, slightly glistening, homogeneous mass with a small, central, teat-like prominence. The appearance of the growths in the tubes, the one from the lip lesion and the other from the interdigital lesion, seemed to be identical (fig. 3). Numerous subcultures were made in each instance and invariably the resemblance was definite. Smears from these cultures revealed round and ovoid, doubly contoured cells with many budding forms, but never any mycelia (fig. 4). Because mycelia had been noted in direct potassium-hydrate

FIG. 3. CULTURES ON SABOURAUD'S MALTOSE AGAR

At the extreme left is a culture, three to four weeks old, from the lip. This growth corresponds with that shown in the middle tube, a culture of the same age from the interdigital web. At the extreme right is a two-week-old culture from the nail-plate.

specimens, it was felt that the organism was a monilia. Sugars were inoculated with material from a culture of the lip lesion and of the interdigital lesion with the result that gas formed in levulose, dextrose and maltose in each instance (fifteen to twenty days' observation). No gas developed in inulin, lactose, galactose, sucrose or raffinose. With these findings it was considered that the organism might be the monilia pinoyi (11).

Histopathology. A biopsy was made of the entire lesion from the left angle of

the mouth. It was fixed in formalin solution and serial sections were cut. About three weeks later the entire lesion at the right angle of the mouth was excised. This material was fixed in Zenker's solution and also cut serially. Sections were stained with hematoxylin and eosin, MacCallum's bacterial stain, the special bacterial stain of Brown and Brenn (12) and with Vierhoff's elastic-tissue stain. In these studies no bacteria were found and nothing could be definitely identified as a yeast-like body.

The histologic study disclosed the following features. The blood vessels of the subpapillary layer of the corium and even a number of those in the deepest portion of the cutis were dilated, and in most instances were filled with red blood cells. The endothelial cells of the intimal linings were clearly defined and the nuclei

FIG. 4. SMEARS FROM THE CULTURES (SHOWN IN FIGURE 3) OF THE LIP (LEFT) AND OF THE INTERDIGITAL LESION (RIGHT). ROUND AND OVAL DOUBLE-CONTOURED BODIES, SINGLE AND MULTIPLE BUDDING FORMS

stained intensely. The connective tissue throughout the zone of reaction, which extended from the basal layer of the epidermis down to the subcutaneous tissue, was quite edematous, stained a faint, pinkish color, was considerably disorganized, and scattered into short or long, narrow, loose, wavy bands dividing or surrounding the masses of intense inflammatory cell infiltrate. The lymph spaces were quite distended with the profuse infiltrate, which, however, was more dense in the area extending downward from the base of the papillary zone than it was in the papillary bodies themselves. The infiltrate was composed for the most part of plasma cells, but there were a number of small lymphocytes, particularly just beneath the rete pegs. Isolated, short strands of clearly staining fibroblasts were present, running perpendicular to the basal layer of the epidermis, but only an occasional fibroblast was noted within the plasma-cell infiltrate.

There was a fairly regular occurrence of a small number of wandering cells, containing a richly staining cytoplasm and in some instances more than one nucleus. A curious feature in the sections from the lesion on the right side of the lips was the presence of lymphocytes as the predominant cell type, and the dispersion of fairly large numbers of large mononuclear wandering cells throughout the infiltrate. A number of these macrophages were filled with well-preserved red blood cells and

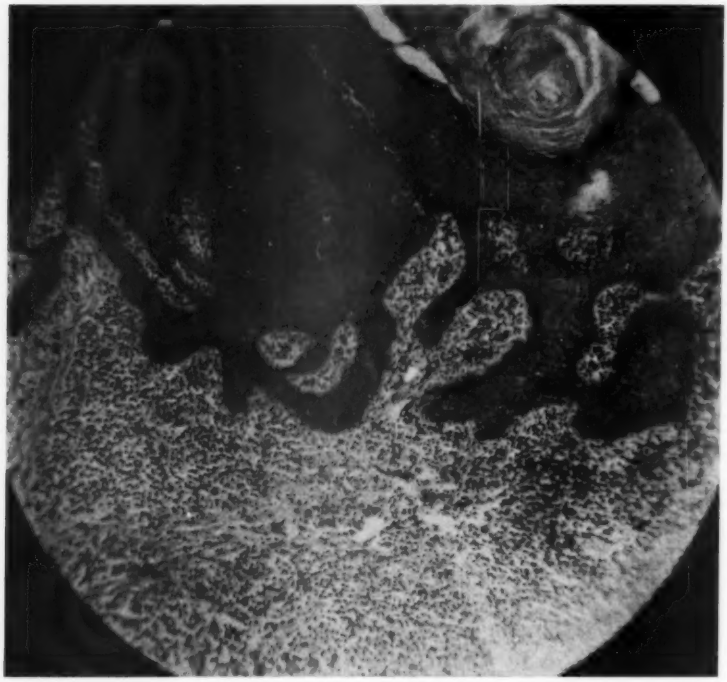

FIG. 5. CHRONIC PERLÈCHE. AN INTENSE LYMPHOCYTIC INFILTRATE FILLING THE LYMPH SPACES AND SEPARATING THE CONNECTIVE-TISSUE FIBERS. MARKED ACANTHOSIS

their nuclei were quite distinct and intact. Trauma could have been responsible for this extravasation of red blood cells. A slight amount of inflammation was present in the subcutaneous layer of connective tissue where a number of vessels were dilated and showed a loosely arranged group of lymphocytes and plasma cells about them. Only an occasional isolated polymorphonuclear leucocyte was found.

The elastic tissue had been displaced completely by the infiltrate in the papillary and reticular layers of the corium. These fibers were fragmented, swollen, deeply-staining, and bunched into ill-defined masses within the bands of connective tissue dividing and surrounding the cellular infiltrate. In the sub-reticular layer the elastic tissue appeared to be intact.

There was a marked acanthosis of very irregular type, many rete pegs extending as far down as the lower third of the cutis and in many instances being extremely

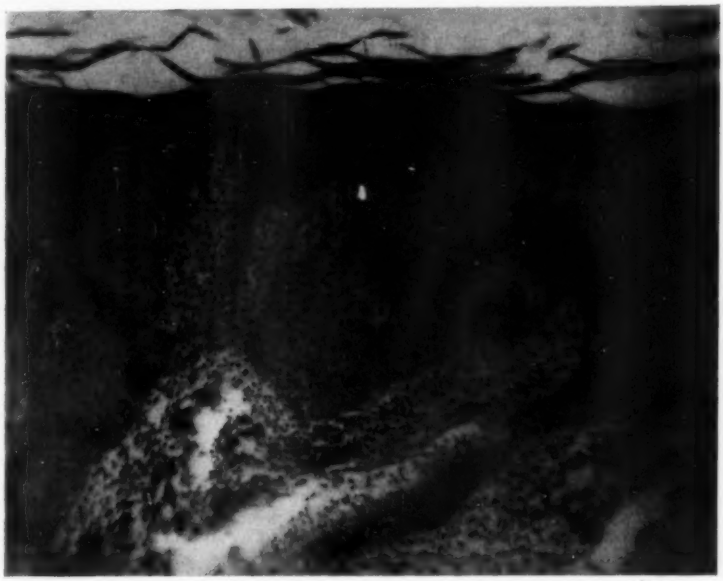

FIG. 6. CHRONIC PERLÈCHE

Note the marked acanthosis and the zone of parakeratosis

broadened, with the formation of sprout-like prolongations which joined across to form a network enclosing islands of connective tissue. The basal layer was for the most part intact, but was not consistently so. Frequently at the tip of a rete peg, and in many instances at the tips of the papillary bodies, there was a disruption of this layer with the dissolution of a number of the cells and replacement by fluid and degenerated cell fragments or lymphocytes, a few of which seemed to invade the prickle-cell layer particularly at these places. The disruption and dissolution involved to a small or moderate degree the lowermost prickle cells adjacent to the basal cells, with the result that some pyknosis and karyorrhexis of

the epidermal cells was in evidence here. In the mid-portion of the prickle layer and even in the outermost region there was here and there some cell vacuolization with loss of cytoplasm, and in the resulting spaces there were deeply staining, distorted nuclei, granules of degeneration and opaque, dust-like nuclear and cytoplasmic grains. The prickle-cell bridges were generally indistinct, but there was no widening of the intercellular spaces. The granular layer was quite intact, stained very distinctly, and perhaps was a bit increased in size. However, in zones directly above papillae which were edematous and filled with inflammatory

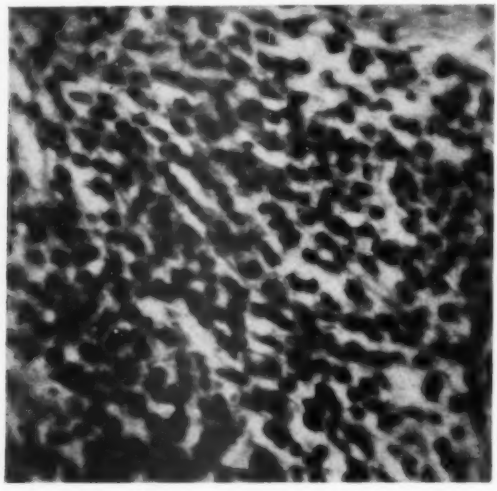

FIG. 7. CHRONIC PERLÈCHE. HIGH-POWER VIEW OF THE SECTION SHOWN IN FIGURE 6

The chronic inflammatory cellular infiltrate is striking. Lymphoid cells are in great preponderance.

cells, there was a replacement of the granular layer by a zone of parakeratosis. Otherwise, there was throughout a slight and sometimes marked thickening of the horny layer (figs. 5, 6, 7, 8).

A case of perlèche of acute type

Case 2. A few months after the above studies had been carried out, a girl, B. S., aged nine years, came into the clinic with the complaint of a sore on the lips and sores on the arms (fig. 9). The lesions had appeared about the same time, which was about two weeks before our examination. The eruption involved the

right commissure and a lesion was located on the anterior surface of each elbow. On the lips the lesion was a fairly well-defined, circular, yellowish, heaped-up crust about the size of a dime when the lips were separated. The lesion covered

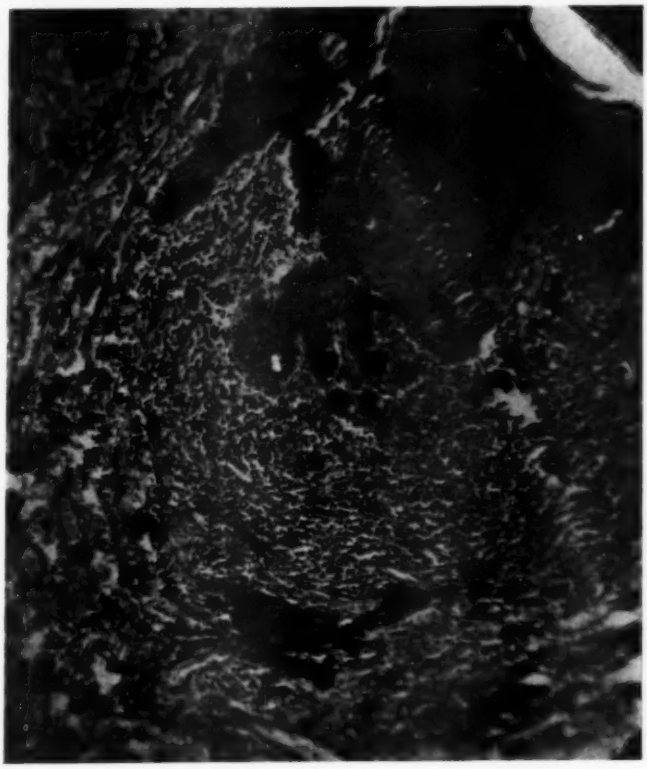

FIG. 8. CHRONIC PERLÈCHE. VIERHOFF'S ELASTIC-TISSUE STAIN

The elastic-tissue fibers have been displaced and apparently destroyed by the granulomatous infiltrate. Note the well-stained band of elastic-tissue fibers in the lower corium.

an area which extended from the vermilion outward over the cutaneous surface for a distance of half a centimeter. The mucous membrane within the vermilion border was not involved. Beneath the crust the skin and mucous membrane were somewhat eroded and of a deep reddish color. A fissure extended through the

involved skin and mucous membrane to the vermilion border. On stretching the lips apart another fissure was revealed from which oozed a serous fluid, but no bleeding was produced by this procedure. There were no lesions elsewhere on the face and none on the scalp. In the bend of the right elbow towards the medial side there was a dry, reddish, slightly scaly, silver-dollar-sized area covered here and there with a few dry yellowish crusts which in one place overlay a superficial, moist, fissured base. A small fading patch of a similar type was present in the bend of the left elbow.

One week later the child returned with a small, yellowish crusted lesion on the commissure at the left angle of the mouth.

FIG. 9. ACUTE PERLÈCHE IN CHILD

Note the erosive, crusted condition at the right angle of the mouth. The disease is only of ten days' duration.

At the time of the first examination scrapings were made of the lesion at the right angle of the mouth and examined in potassium hydrate solution with negative results. Material from the lesion was inoculated in five tubes of Sabourand's maltose agar. One tube remained sterile, but after three or four days there developed in each of the other four tubes small, smooth, whitish colonies, which later coalesced to form a smooth, elevated, slightly shiny mass. In one tube one isolated colony developed a greyish, opaque appearance. Smears from these cultures showed staphylococcus albus in predominance and some growth of a diphtheroid. However, from one tube a beta streptococcus (hemolyticus) was obtained and in subcultures appeared in pure form. Not in a single instance was a yeast-like organism found.

COMMENT

In view of the fact that the studies made are based on the findings in but two cases, the conclusions drawn must necessarily be very modest in scope. It is difficult to attach a primary etiologic significance to the organisms found in scrapings or cultures from the lesions of perlèche. The normal mouth harbors the various cocci which have been found in these cases and, as brought out before, the fungi are frequent inhabitants of the normal skin. It is quite likely that the angles of the lips become a suitable terrain for the multiplication of any one or a number of these organisms when they are traumatized or irritated by bad teeth, tooth-brushes, excessive salivation or poor hygiene. The primary invader could, therefore, be a coccus or a yeast-like organism or both, and either of these might become predominant. In some instances a fruitful source may exist for the implantation of an active organism on the lips as, for example, in the cases of perlèche associated with lingual, interdigital, and paronychial moniliasis reported by Robinson and Moss (13) and in the case with a fairly generalized cutaneous moniliasis reported by Hopkins (14). Sabouraud (15) was of the opinion that perlèche is not uncommonly associated with impetigo and he would, therefore, attribute the disease to a streptococcus. In case 1, yeast-like organisms were cultured with ease from the perlèche lesions and these organisms were apparently identical in every respect with those obtained from the web of the fingers. It is quite probable that the disease in the web, since it preceded that on the lips, was the source of the infection of the lips. Cultures on Sabouraud's maltose agar from the perlèche in the child, however, yielded no yeast-like organisms, but instead staphylococci and streptococci.

From a study of the literature and the findings in these two cases, it would seem that perlèche is usually produced primarily by either one or both types of the common cocci or by a yeast-like organism. Secondary invaders could, of course, crowd out the primary agent and it is not unlikely that the former might occasionally maintain the disease in a chronic state. The specificity of the etiologic agent in certain cases can, of course, not be questioned since Finnerud (6) reproduced it with yeast-like organisms. It appears, however, that,

broadly speaking, the condition can be caused by any one or perhaps more than one of several different types of organisms. It would perhaps be simply a matter of chance as to what type of organism gained entrance into a suitable terrain at the commissure of the lips and perhaps also a matter of peculiar local susceptibility. In the case of the adult (case 1) the yeast-like organisms, because of their great predominance, probably were concerned either primarily or secondarily in maintaining the perlèche in a state of activity. With regard to the case of perlèche in the child (case 2) of only two weeks' duration, the important point is that no yeast-like organisms could be grown in culture. It would seem, therefore, that even if the staphylococci or streptococci obtained in this case were not etiologic, this fact would serve to indicate at least that yeast-like organisms are not to be held responsible in all cases of perlèche.

It is rather difficult to explain the absence of demonstrable organisms in the microscopic sections unless they were so superficially situated that most of them were removed in the process of fixation and staining.

CONCLUSIONS

1. A specific etiology of perlèche has not been determined.
2. A case of chronic perlèche in an adult is reported, and also one of an acute type in a child.
3. A survey of the literature and the cultural study of the two cases would suggest that perlèche may be primarily produced either by streptococci and staphylococci or by a fungus organism. However, there remains the possibility that an as yet undiscovered virus is the primary agent and that these organisms are secondary invaders.
4. The histopathology of the case studied showed a chronic granuloma.

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A NOTE ON THE COMMUNICABILITY OF COLDS[1]

PERRIN H. LONG, M.D., ELEANOR A. BLISS, D.Sc., AND HARRIET M. CARPENTER, PH.B.

From the Department of Medicine, Johns Hopkins University

It is generally accepted that the common cold is extremely contagious during the primary stage of the affection. As yet, however, no evidence has been adduced that colds may be infectious during the incubation period before the onset of any clinical symptoms or signs of the disease.

Recently, we were able, by chance, to make certain observations upon this point. One of us is in the habit of taking weekly cultures from the rhinopharynges of chimpanzees which are being used as experimental subjects in certain investigations on upper respiratory disease. These apes are kept in isolation cages and the attendants and observers don masks and gowns and wash their hands thoroughly before coming in contact with the animals. This isolation has usually been effective in preventing respiratory infections in the past and was effective in preventing the spread of colds to other animals after the outbreak of the upper respiratory infection which is to be described.

On the morning of March 14, 1932 the weekly routine throat cultures were made upon 9 of our 11 chimpanzees by one of us. The observer, accompanied by an attendant, entered the cage of ape A, which was the third animal visited during the morning. This ape was very tractable and the throat culture was easily obtained. Following this, four other apes were visited. In the afternoon cultures of the throats of two more apes were taken. The first animal visited at this time, ape B, is a large female, and at the time of the culture was quite intractable and had to be held by the attendants. The observer, on entering the cage, neglected to adjust her mask over her face. Some difficulty was experienced in getting this ape's mouth open and the observer

[1] This investigation was supported by a grant from the John J. Abel Fund for Research on the Common Cold.

came in very close contact with the animal. When the procedure was about completed, an attendant called the observer's attention to the fact that her face was not covered by the mask. This break in technique was corrected after the completion of the culture and another ape was visited.

At this time all of the apes were in good health and had been free from any signs of upper respiratory infection for a period of over two

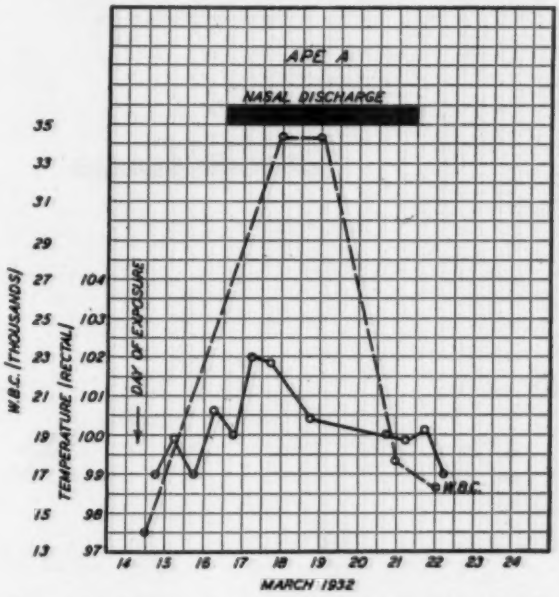

CHART I. CLINICAL COURSE OF THE INFECTION IN APE A

months. Individually, ape A had been free from respiratory disease for exactly two months and ape B for two and one-half months. There had been no untraceable respiratory infections in the colony since July 1931.

The bacterial flora of the rhinopharynges of these two animals had been similar and constant for the preceding month and showed the following microörganisms: Alpha, Beta and Gamma streptococci, gram-negative cocci, Pfeiffer's bacilli, staphylococci, diphtheroids, and

pneumococci. No demonstrable qualitative change in the bacterial flora was noted either before or after the occurrence of the upper respiratory infection.

During the month of March, 1932 none of the observers or attendants had any type of upper or lower respiratory infection, with the exception of the infection in the observer who came into contact with the animals on March the fourteenth. On the afternoon of March

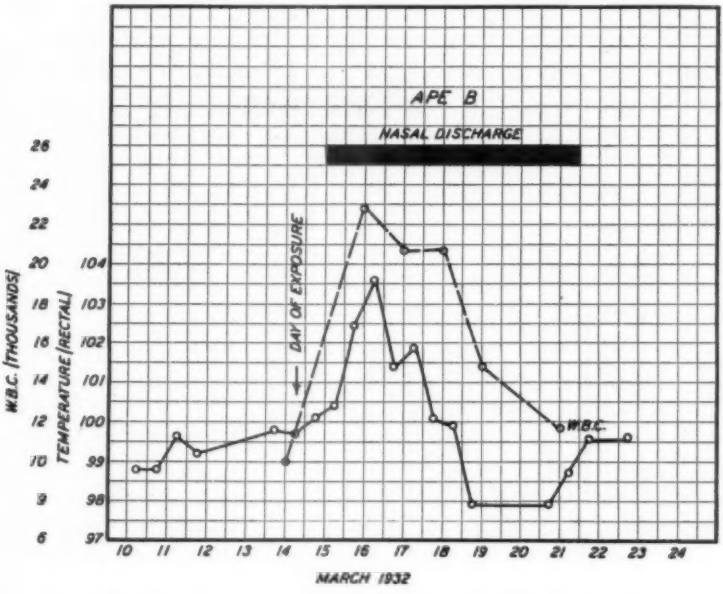

CHART II. CLINICAL COURSE OF THE INFECTION IN APE B

the fifteenth this individual complained of sneezing, lacrimation, conjunctival irritation, and a sense of fulness in the rhinopharynx. A small amount of watery nasal discharge was present. On the following day this person was suffering from a typical common cold, which lasted for two weeks and which was of a severe type.

On March the sixteenth, two days after the chimpanzees had been visited by the observer who subsequently developed a cold, two of the

nine animals, apes A and B, developed nasal discharge, elevation in temperature, increased total white blood cell counts, and nasal obstruction. These signs and symptoms lasted for several days and both apes passed through the typical stages of a common cold.

The clinical course of these infections is outlined in charts I and II. No other primary infections developed and there were no secondary cases in the ape colony.

DISCUSSION

We are frequently impressed by the observation that many individuals who are suffering from typical common colds cannot remember any contact with individuals suffering from a similar infection. Other contagious diseases, such as measles or chicken-pox, are known to be highly infectious late in the incubation period or during the prodromal stages. It has been thought that possibly the common cold might also be contagious before the actual onset of symptoms. The testing of this belief is not feasible because it does not lend itself easily to experimental procedures. We believe that the observations just recorded offer some evidence upon this point because, under controlled conditions, two of nine chimpanzees developed typical common colds following contact with an individual who was late in the incubation stage of a common cold. It is obvious that ape B might have received her infection through a more or less direct contact with the unmasked observer, but in the case of ape A the observer was masked; hence it seems improbable that masking is a complete protection against the dissemination of the infectious agent, although it may interfere so that contact infection is less likely. The possibility of the observer having contaminated her hands by unconsciously touching her face after having scrubbed them, must be considered. These findings illustrate forcibly the difficulties in preventing upper respiratory infection, even though strict precautions for the protection of a given group of chimpanzees are in effect.

SUMMARY

By a chance observation made under controlled conditions, it seems possible that at times the common cold is transmissible during the incubation period.

THE USE OF IODINE IN THE PRE-OPERATIVE TREATMENT OF HYPERTHYROIDISM; WITH REMARKS ON IODINE REMISSIONS AS OBSERVED IN BALTIMORE, MD.[1]

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Iodine has now an accepted place in the regimen of pre-operative treatment of hyperthyroidism in this country. Its value is undisputed and numerous careful reports testify to its efficacy and describe the results of its administration. Much has been written concerning the use of iodine but little concerning its misuse.

In the fundamental papers of Plummer and his associates (9, 11, 1) of Means and his associates (14, 8), of Mason (6) and of Starr (13) full descriptions have been given of the nature of the "iodine remission" in hyperthyroidism.[2] Although these facts are in constant use in the large thyroid clinics of this country, many physicians are apparently unaware of them and continue to prescribe iodine haphazardly and without plan. In cases of hyperthyroidism that are severe enough to warrant surgical measures such a misuse of iodine may rob the patient of full benefit from the drug and expose him to unnecessary risk. It is the purpose of this paper to re-emphasize the important points relating to the use of iodine in hyperthyroidism as illustrated by the material at the Johns Hopkins Hospital. A comparison will be made also between the character of the response to iodine as observed in Baltimore and that observed in Boston by Means and others (8) and in Ann Arbor, Michigan, by Coller and Potter (2).

The present report includes a study of the iodine response in 157 cases of hyperthyroidism in which the data recorded were sufficient for accurate deductions; otherwise there has been no selection of material.

[1] Submitted for publication May 1, 1932.

[2] The history of the use of iodine in hyperthyroidism is covered in the excellent papers of Marine (5), Boothby (1) and Thomas and Rienhoff (16).

In each instance, determinations of the basal metabolic rate were made one or more times before the administration of iodine and several times during the period of its administration. The duration of bed rest before iodine was begun varied from one day to several weeks. Iodine was given in the form of Lugol's solution and usually in doses of 1 cc. t.i.d.

This series is comparable to that of Means and his associates (8) and that of Coller and Potter (2) save that no attempt has been made in the present report to classify the cases under the headings "exophthalmic goitre" and "adenomatous goitre with hyperthyroidism." Such a distinction would be easy in the more easily defined cases but difficult in others. In this clinic a large number of cases are seen that embody many of the characters of both exophthalmic goitre and of adenomatous goitre with hyperthyroidism. These facts have led to the conception that the two conditions are probably but different manifestations of the same disease and that the ultimate picture depends on such factors as age of onset, severity of the disease, occurrence of natural remissions and the type of patient in which the disease occurs. Rienhoff (12) and Thomas (15) have discussed these points in previous reports from this Hospital.

POINT OF MAXIMUM RESPONSE

Within 48 to 72 hours after the institution of iodine in cases of hyperthyroidism, signs of definite improvement become evident. The nervousness, emotional instability, tachycardia and increased basal metabolism abate and all the phenomena of the disease become less marked. This improvement continues for a period varying from 8 to 18 days and occasionally for longer. In the present series the point at which maximum improvement occurred under iodine varied from 5 to 32 days after institution of the drug. In the large majority of cases, however, this point was reached between the 9th and 14th day, and more frequently on the 10th day than on any other. This is well illustrated in figure 1. The average time for the entire series before this point was reached was 13.5 days. The point of maximum improvement was estimated by fall in pulse rate and in basal metabolic rate, by gain in weight and by lessening of the signs and symptoms of the disease.

The above results are in agreement with the series of cases of exophthalmic goitre reported by Means and others (8) from Boston and by Boothby (1, 9) from the Mayo Clinic, in which the point of maximum improvement occurred, respectively, at 10 days and 8 days after the institution of iodine. Coller and Potter (2) at Ann Arbor, Michigan, have shown that the response to iodine in cases of exophthalmic goitre drawn from a goitre area is slightly less marked and that the point of maximum improvement is later—falling between 14 and 16 days after

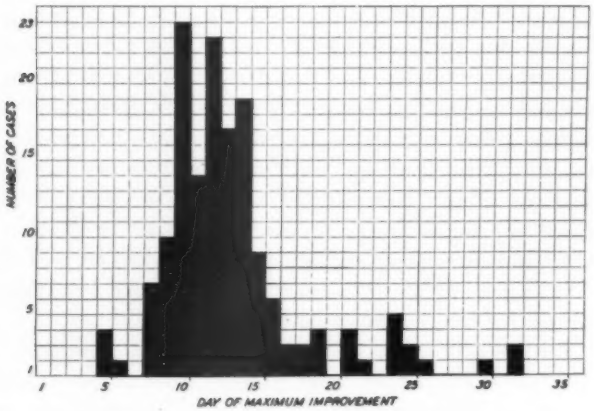

FIG. 1. DAY OF MAXIMUM IMPROVEMENT

This illustrates that 80 to 90 per cent of the 144 cases of hyperthyroidism showed their maximum improvement under iodine therapy on or between the 8th and 15th day; that the majority attained this state on or between the 10th and 14th day, but that several cases exhibited a slow response.

the institution of iodine. Furthermore, their evidence would suggest that the disease exists in a more severe form in such a locality than it does in the coastal areas from which the majority of cases in the Boston and Baltimore series are drawn. In respect to the severity of the disease, as measured by the initial basal metabolic rates, the Boston and Baltimore series are almost identical.

Figure 2 depicts the degree of fall of basal metabolic rate in 102 cases of the present series, following institution of iodine therapy. The greatest reduction is seen to have occurred in the cases that presented

the highest initial basal metabolic rates; the average drop, however, for each group amounts to approximately 50 per cent regardless of their initial height. It is to be noted also that the point of maximum im-

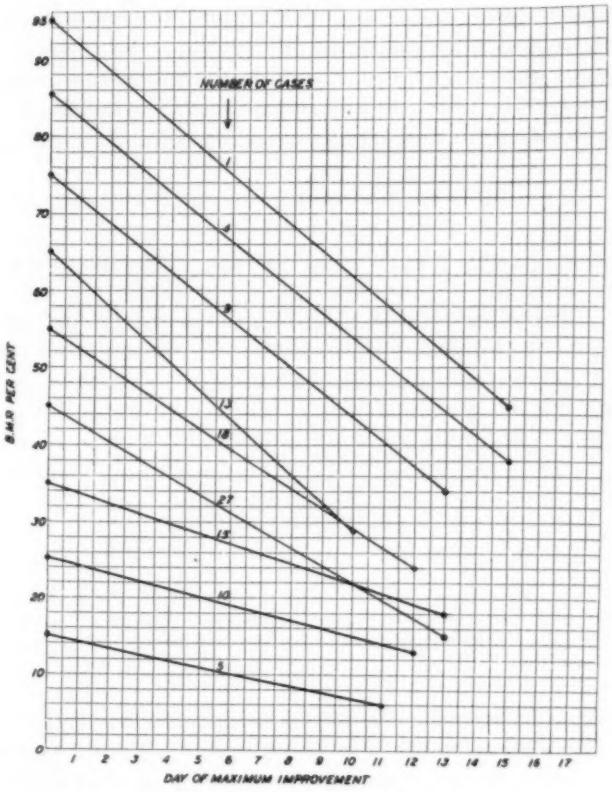

FIG. 2. RESPONSES TO IODINE IN HYPERTHYROIDISM

Basal metabolism before compared with that after iodine medication; in 102 cases of hyperthyroidism divided into groups according to pre-iodine level, each ten points representing a level.

The declivity of the curves are in general related to initial height; the higher the initial rate, the sharper the fall. The average drop, however, for each group amounts to approximately 50 per cent regardless of their initial height. This compares closely with the series reported by Means.

provement under iodine was reached sooner in the cases having the lowest initial basal metabolic rates. These features are in agreement with those of the previously reported series of cases.

In Table 1 the series of cases from Baltimore, Boston and Ann Arbor are compared with respect to the degree of remission obtained under iodine and to the time necessary for the full development of the remission. The extent of the fall in the metabolic rate in each group is seen to be almost identical in the present series and in Means' series. The responses in Coller and Potter's cases were obviously not so striking.

TABLE 1

GROUP BY B. M. R.	PRESENT SERIES (102 CASES)			MEANS' SERIES (128 CASES)			COLLER AND POTTER'S SERIES (128 CASES)		
	Number of cases	Fall in B. M. R.	Days	Number of cases	Fall in B. M. R.	Days	Number of cases	Fall in B. M. R.	Days
per cent									
90–100	1	50	15						
80–90	4	48	15	8	51	10	5	48	17
70–80	9	41	13	8	51	10	21	27	12
60–70	13	36	10	22	39	10	27	25	14
50–60	18	29	12	25	31	10	25	16	14
40–50	27	30	13	32	27	9	27	15	12
30–40	15	17	13	26	20	8	17	12	16
20–30	10	12	12	7	8	8	6	8	10
10–20	5	9	11						

Tabular comparison of reactions to iodine in Means and associates' (8) and Coller and Potter's (2) series of cases of exophthalmic goitre and the present series of unselected cases of hyperthyroidism.

The point of maximum improvement under iodine in the present series of cases was later than in Means' cases. (It is not improbable that the point of maximum improvement in both series might have been attained one or two days earlier than represented had daily metabolic determinations been made. Such a procedure is practically impossible in a large series of cases selected from the general wards; an opinion previously expressed by Means and his co-workers in respect to the Boston series. This question of the exact day of maximum improvement indicates, therefore, a possible error common to both the Boston and Baltimore series and thereby permits their com-

parison.) This has caused a slight flattening in the declivity of the curves in figure 2 and might be thought to be due to the inclusion of some instances of nodular goitre in the present report. The average point of maximum improvement in 13 cases of nodular goitre with hyperthyroidism (13.3 days) was, however, substantially the same as that for the entire series (13.5 days). It should be pointed out that the extent of the fall of the basal metabolic rate is similar to that observed by Means.

TEMPORARY NATURE OF IODINE REMISSION

The remission obtained from iodine is not sustained. If the drug is discontinued the basal metabolic rate and pulse rate rise rapidly after a variable and unpredictable interval (Starr's post-iodine reaction (13)), and all the phenomena of the disease return—often with a severity greater than before. On the other hand, if iodine is continued past this point of maximum improvement there is a gradual recurrence of signs and symptoms of the hyperthyroid state and the basal metabolic rate (and usually the pulse rate) climb again despite continuance of the drug in the same or larger doses. Recurrence then of hyperthyroidism follows after the initial remission either with or without the continued administration of iodine. These two undesirable phases in the reaction of the disease to iodine were early reported by Means and his associates (14), and later were illustrated and reemphasized by Starr (13) as potent limitations and warnings in the use of the drug. Recently, further study and discussion of these two important points have been issued and the latter reaction, namely, recurrence during prolonged administration of iodine has been termed "Refractoriness to Iodine" (19) (see fig. 3). In very occasional instances the remission persists for several weeks, even after withdrawal of the iodine.

It is obviously of great importance to the patient that iodine be given according to a definite plan and that, especially in severe cases, operation be performed at the most favorable period. An optimistic but mistaken postponement of surgical procedures is not infrequently seen. Once the point of maximum improvement has been passed a remission of similar degree can be obtained only by discontinuing the iodine for a period of weeks or even months and allowing the phenomena of the

disease to reappear. Iodine can then be administered and a satisfactory remission obtained in most instances. Figure 4 illustrates the production of a remission with iodine in a case of exophthalmic goitre. Operation was delayed for too long a time. During a later remission induced by iodine, (which was less marked, however, than the initial remission) subtotal thyroidectomy was successfully performed.

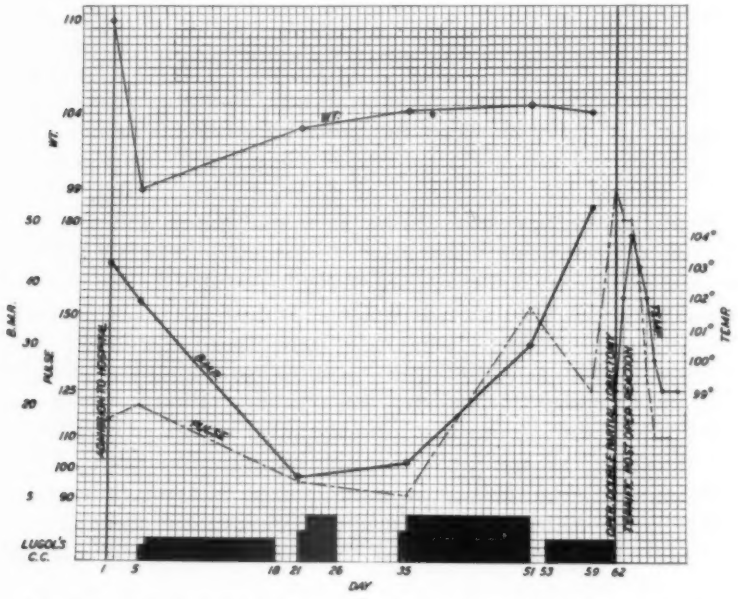

FIG. 3. REAPPEARANCE OF SYMPTOMS DURING PROLONGED USE OF IODINE

Case No. 23,668, female, 52, exophthalmic goiter. Typical iodine remission obtained in 21 days; in spite of continued medication a relapse ensued with sharp increase of pulse and basal metabolic rate; operation two months after the initial iodine remission was attended by severe reaction.

A decision should be made as to whether the patient is likely to be ready for operation when the peak of the iodine remission is reached. This decision should be made before any iodine is administered. There is little rationale in giving iodine as a pre-operative measure in a

given case until it is apparent that the patient will be ready for operation at the time of the expected iodine remission.

There are numerous reasons why it may be wise to delay the institution of iodine therapy. Great emaciation, local infections of the teeth

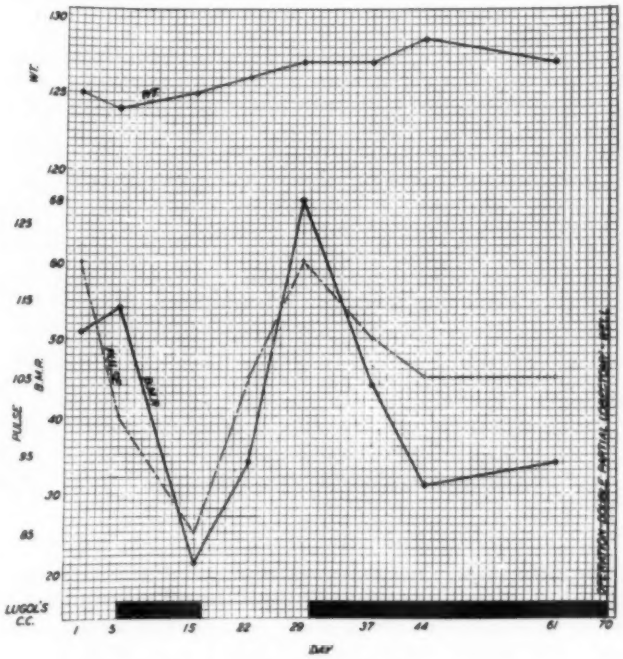

FIG. 4. SECONDARY REMISSION UNDER IODINE

Case No. 1365, female, 35, exophthalmic goitre. First remission was typical; the point of maximum improvement occurred on the 10th day; iodine was then withheld, and there occurred a sharp increase in pulse and basal metabolic rate, but a continued gain in weight. After an interval of 2 weeks iodine was again administered but the resulting remission was less striking than the initial one.

and gums or of the upper respiratory tract, certain cardiovascular complications and other factors may make it the course of wisdom to prescribe preliminary bed-rest, sedatives, high caloric diet and appropriate local treatment, if infection is present, before the iodine is com-

menced. We have gained the impression that the ultimate degree of improvement exhibited in moderately severe or severe hyperthyroid cases is greater at the end of the iodine remission when a preliminary period of general medical treatment precedes the administration of iodine; on this basis, at the present time, such a regime is

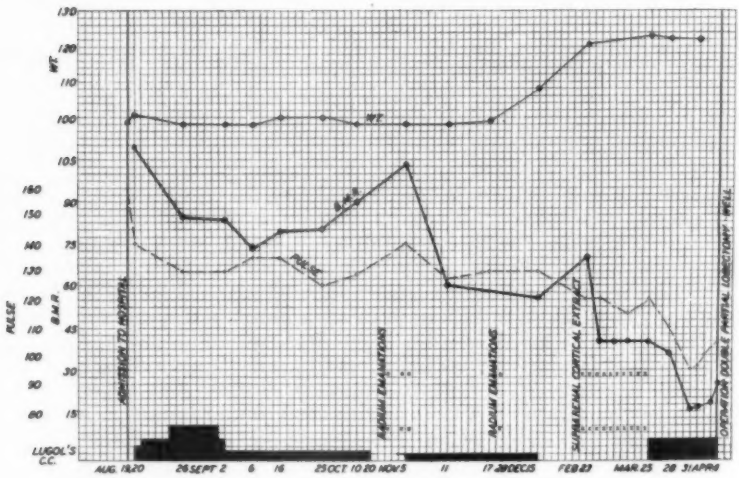

FIG. 5. IODINE—THE FINAL PRE-OPERATIVE THERAPEUTIC AGENT

Case No. 32,711, female, 21. Severe case of exophthalmic goitre. A course of iodine had been administered before admission to hospital, making it not unlikely that relapse with aggravation of hyperthyroidism was in progress when first examined. Two months' administration of iodine of no avail; later radium emanations proved of questionable value; second course of iodine for 41 days ineffectual; administration of suprarenal cortical extract appeared to cause some improvement. Finally, after almost 8 months of hospitalization (during the last 3 months of which iodine was withheld), Lugol's solution elicited an excellent remission. Operation was attended by no untoward reaction.

followed, unless contraindicated, on the general wards of the Johns Hopkins Hospital. Looked upon in this light iodine is used as a means to supply the final impetus for the pre-operative preparation of the patient. Figure 5 illustrates this point and also the fallacy of employing iodine too soon. Although what might be interpreted as a slight

remission was obtained, the patient was still too sick to be operated upon. After prolonged general medical treatment and specific therapy of questionable value, a later remission with iodine was obtained and operation was successfully performed.

SLOW IMPROVEMENT UNDER IODINE

It must not be thought that the remission from iodine is maximal within two weeks in every case. There are fairly frequent instances in which improvement continues up until a month or more after the institution of iodine (see fig. 6).

In the present series of 157 cases, 34 patients continued to show improvement under iodine when the drug was administered beyond the usual period of two weeks. In a number of other patients that were operated upon within two weeks after the institution of iodine it is possible that further slight improvement might have occurred under iodine had operation been delayed. Although such exceptions exist, the burden of responsibility rests upon the physician who allows operation to be delayed beyond the *usual* point of maximum improvement. Such instances are not infrequently seen in dispensary practice when iodine is administered to ambulatory patients suffering from moderate hyperthyroidism. Following the iodine remission the symptoms gradually return and the necessity or the wisdom of operation becomes apparent. The surgeon has been robbed, however, of the most potent single agent in the pre-operative preparation of the case and a prolonged period of special care without iodine becomes necessary before the drug can be used again to good effect.

Thompson and others (18) who made a careful study of 24 patients with exophthalmic goitre under treatment with iodine for prolonged periods of time, concluded that the response, favorable or unfavorable, seemed to be determined more by what was occurring during the natural course of the disease spontaneously than by any influence attributable to the iodine itself. Only nine cases (all mild) of their entire group exhibited a satisfactory response, an observation which drew forth the following conclusion: "At present there is no way of predicting definitely in any given case what the response to such treatment will be."

This conception of the action of iodine has led many conservative

observers to restrict its use in hyperthyroidism almost entirely to the pre-operative preparation of patients and to the amelioration of post-operative reactions. Again, in reference to the use of the drug in

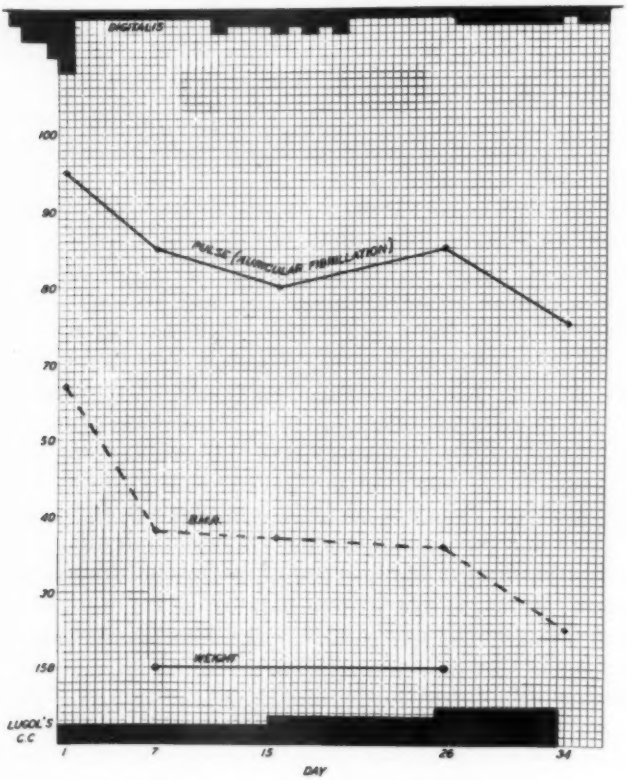

FIG. 6. SLOW RESPONSE TO IODINE

Case No. 6317, female, 38, exophthalmic goitre with auricular fibrillation. There was slow improvement under influence of iodine, the point of maximum improvement not being reached until the 34th day.

hyperthyroidism as a treatment *per se*, Means (7) has said: "The fact that exophthalmic goiter starts with a mild course is no guarantee that it will so continue, and in practically every instance where, because of

the apparent mildness of the disease, we have carried on with iodine alone, we have later regretted having done so."

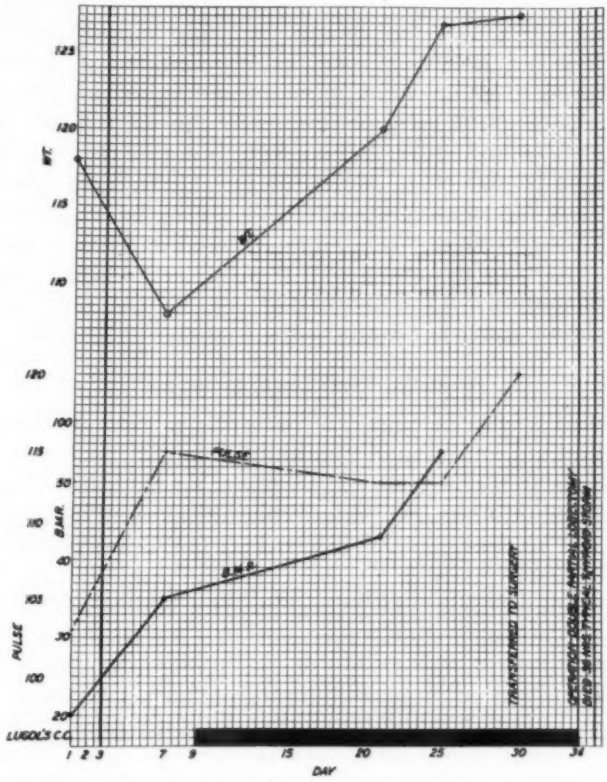

FIG. 7. UNFAVORABLE COURSE DURING IODINE THERAPY

Case No. 9925, female, 24, illustrates a rare occurrence during iodine therapy. Typical history of exophthalmic goitre of 6 months' duration without any previous iodine medication. A steady intensification of the signs and symptoms of the disease occurred save for a progressive gain in weight; patient died in severe postoperative toxicosis.

INTENSIFICATION OF SYMPTOMS DURING IODINE THERAPY

There can be no doubt that in occasional instances the symptoms of hyperthyroidism become more marked during the administration of

iodine. In the present series, 4 patients were encountered who exhibited an increase in the severity of symptoms during its use. A discouraging example of this type of response is illustrated in figure 7. This patient had received no iodine before admission to the hospital. Coincidently with the administration of iodine the evidences of hyperthyroidism increased and following operation a terrific thyroid-storm occurred that resulted in the patient's death. We regard instances such as this as occurring despite the use of iodine rather than because of it. Similar unfavorable reactions have been observed by Means and others (14) and recently by Thompson and others (18) in two cases. The latter observers noted, however, that this lack of response which they term "refractoriness to iodine" may be only temporary and that withdrawal of iodine for one to two months is sometimes followed by a typical iodine remission.

NEGATIVE INFLUENCE OF IODINE

Iodine in a small percentage of cases fails to exert any influence whatsoever on the status of hyperthyroidism. Of this series, nine cases (of the mild type) were entirely refractory and failed to respond one way or another. Analogous observations were reported by Means and his associates (14) (Their chart 11–5 cases) and by Starr (13) (His chart 3–7 cases).

In those instances in which iodine appears to have had either a negative or a deleterious effect it is possible that the patient may have received iodine and experienced a remission prior to admission to the hospital. In such an instance observation of the patient would commence at the end of the remission and the administration of iodine at such times would appear to have either a bad effect or temporarily no effect at all. This point has been emphasized by Graham (3) and there can be no doubt that such an explanation holds true in some instances, but isolated cases do occur, however, which cannot be explained on such a basis (an example of which has already been seen above).

IODINE IN NODULAR GOITRE WITH HYPERTHYROIDISM

In the present series the response to iodine in cases of nodular goitre with hyperthyroidism has not been less striking or more uncertain than in straightforward cases of exophthalmic goitre.

As a result of Plummer's conception of exophthalmic goitre and of toxic adenoma it was at first thought that iodine was contraindicated in cases of adenomatous goitre with hyperthyroidism. He felt that exophthalmic goitre was characterized by the excessive output of an abnormal and incompletely iodized secretion of the thyroid gland whilst "toxic" adenoma was a "pure" hyperthyroidism associated with the output of excessive amounts of the normal secretion of the thyroid gland. In the former condition iodine was thought to act beneficially by supplying the iodine-deficient secretion with a necessary element but in the latter condition there was thought to be a danger of it increasing the degree of hyperthyroidism. From the available and probably adequate evidence, it would now seem that satisfactory remissions may be obtained in many instances of nodular goitre with hyperthyroidism by the use of iodine. Graham (3), Starr (13), and Yeomans and Kampmeier (20) were able to find no fundamental difference in the reaction to iodine of cases of exophthalmic goitre and of nodular goitre with hyperthyroidism provided the drug had not been administered immediately before the time of observation.

In the present series of 157 cases of hyperthyroidism, the majority of which were exophthalmic goitre, there were altogether 14 instances in which the clinician and the pathologist agreed upon the diagnosis of nodular goitre. In 10 of these 14 cases excellent remissions were obtained from iodine; in 3 cases the remissions were satisfactory but did not equal in degree the average remissions illustrated in figure 2; in the one remaining case an increase in the symptoms and in basal metabolic rate occurred during the time of administration of iodine. In these cases the average period of bed-rest and observation before the institution of iodine was $8\frac{1}{2}$ days. In the 13 cases that showed a favorable response to iodine the point of maximum improvement was reached, on the average, in 13.3 days. The average point of maximum improvement for the entire series of 157 cases of hyperthyroidism was 13.5 days.

It is recognized that such satisfactory responses to iodine in nodular goitre with hyperthyroidism may not be encountered in other parts of the country. Certainly in the 50 cases studied by Coller and Potter (2) 46 per cent failed to show a favorable reaction to the drug. On the other hand, Yeomans and Kampmeier (20) found, in an unselected

group of 30 cases from the same goitrous area, the same degree and percentage improvement (75 per cent) as obtained in a general group of exophthalmic goiter. Moreover, Starr (13) could determine no essential difference in the responses of two similar groups observed in Chicago.

IODINE PREPARATIONS AND ADMINISTRATION OF IODINE

Since the early papers of Plummer, iodine has been administered to patients with hyperthyroidism almost entirely in the form of Lugol's solution.[3] This preparation which, as Boothby (1) has said, was chosen "somewhat arbitrarily" has been inflicted upon patients ever since, and, despite its objectionable taste and tendency to stain the teeth, it is still the most popular preparation. Although it has long been thought that other iodine preparations would be equally efficacious, the recent work of Lerman and Means (4) relieves the matter of all doubt. These investigators have shown, that potassium iodide by mouth and even ethyl iodide gas by inhalation give rise to iodine remissions, in exophthalmic goitre, exactly similar in kind and degree to those obtained from adequate doses of Lugol's solution by mouth.

In a recent study of the effective range of iodine dosage in exophthalmic goitre, Thompson and others (17) have shown that, in Boston, maximal iodine remissions can be obtained with Lugol's solution administered in doses of 1 drop (6 mg. iodine) daily. Although such small doses are not recommended, it would seem probable that the extremely large doses administered in many clinics are excessive and unnecessary. Marine (5) has emphasized this point frequently. It is probable that the administration of Lugol's solution in doses of 5 to 10 drops daily (30–60 mg. iodine) or potassium iodide in doses of 3 to 6 grains daily (0.18 to 0.36 gm.) is more than adequate and allows a wide margin of safety. Potassium iodide or sodium iodide, in aqueous solution, has proven a very satisfactory form in which to administer the drug and although both of these salts are rather unpleasant to the taste they have a considerable advantage over Lugol's solution in this respect. We have obtained maximal remissions in 5 patients with hyperthyroidism to whom potassium iodide has been administered in

[3] Iodine, 5 per cent, and potassium iodide, 10 per cent, in aqueous solution.

doses of 15 grains (1.0 gm.) daily. As Means (7) has pointed out, however, no harm results from excessive doses and it is better to err on this side than to give too little of the drug. Further studies of the minimal effective dosage of iodine, similar to those of Thompson and others (17) in Boston, should be made in various widely separated parts of the country, in order to establish sound standards for the administration of the drug.

SUMMARY

The data on 157 cases of hyperthyroidism treated with iodine are analyzed and presented. The division of the series into the exophthalmic type and nodular goiter with hyperthyroidism was not made because features of each type were observed frequently in the same patient.

One hundred and forty-four cases responded with definite iodine remissions, the point of maximum improvement being reached on or between the 8th and 32nd day; the greatest number reached this point on the tenth day; the average for the entire series was 13.5 days. As a rule, mild cases presented their remission one or two days earlier than the more severe. An average decrease of 50 per cent in the metabolic rate was obtained regardless of its initial level prior to iodine therapy.

These studies correspond closely to the series reported by Means and others from Boston, except that in the latter city remissions were reached one or two days earlier; in contrast, however, the series from Michigan, a goitrous area, reported by Coller and Potter, responded less favorably than either the Boston or Baltimore cases.

No essential difference between cases of exophthalmic goiter and nodular goiter with hyperthyroidism in their reaction to iodine was noted. Of the 14 cases of the latter type, included in the general series, 13 showed remissions similar in rate and degree to those exhibited by the entire series. This fact coupled with observations reported from other clinics of the country strengthens the growing conception that only one type of hyperthyroidism exists, and that typical remissions with iodine in the majority of instances can be obtained in the nodular group as well as in the exophthalmic type.

Several reactions to iodine are illustrated: (1) Slow prolonged

improvement; (2) Reappearance of signs and symptoms of the disease during prolonged administration; (3) Two consecutive remissions occurring in the same patient with only a short inter-iodine period (2 weeks); (4) Iodine—the final pre-operative therapeutic agent; (5) Exacerbation of the disease coincident with iodine administration.

Because of the temporary nature of the iodine remission, emphasis is placed on the advisability of administering iodine according to a definite course with operation almost without exception definitely in mind. A preliminary pre-iodine period of general medical care, we believe, will produce a greater ultimate improvement than that obtained by merely iodine alone. There is increasing evidence to the effect that iodine should be restricted with few exceptions to the pre-operative preparation of the patient.

The dosage of iodine and the various forms in which it may be given are commented on.

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ACUTE EXPERIMENTAL GLOMERULITIS FOLLOWING INJECTION OF STREPTOCOCCUS VIRIDANS INTO THE RENAL ARTERY[1]

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In view of the fairly well established connection between streptococcal infections and acute glomerular nephritis, many investigators have attempted in recent years to produce similar experimental glomerular lesions in laboratory animals by means of various streptococci or their products.

The present article is a direct continuation of the work previously reported from this laboratory by Lukens and Longcope (1) on the production of renal lesions in rabbits by means of the B-hemolytic streptococcus. They found widespread glomerular inflammatory lesions within a few days following the injection of killed suspensions of B-hemolytic streptococci directly into the renal artery. It was intimated that this may possibly be dependent on the presence of an allergic state in the affected kidney, since it was shown that glomerulitis was much more frequently produced in animals which had previously been "sensitized" by being subjected to streptococcal skin infection. Lukens (2) subsequently reports almost identical lesions in rabbits following the third successive injection of B-hemolytic streptococci into the renal artery. In view of the satisfactory results obtained in these experiments, it was thought that it might be a matter of interest to ascertain if similar lesions could be obtained by the use of green streptococci, and, if so, to enquire more fully into the question of what factors might predispose to the production of such an acute streptococcal glomerular lesion.

The literature on experimental nephritis is briefly discussed in the above article by Lukens and Longcope and mention need here be made only of subsequent reports. Blackman, Brown and Rake (3),

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by intravenous injection of pneumococcal autolysate, produced glomerular hemorrhages with capsular adhesions and crescents, as well as degenerative and necrotic changes in the tubules. Bell and Clawson (4) gave repeated intravenous injections of streptococcus viridans into a monkey over a period of four years and produced anatomical lesions resembling the "human lipoid nephrosis of mixed type." Duval (5) recently reports hemorrhagic and degenerative glomerular changes with subsequent crescent formation and fibrosis in dogs following intraperitoneal or intravenous injection of killed scarlatinal streptococcus or its "lysate."

The present experiments were undertaken to determine if, by using the method of Lukens and Longcope, as satisfactory renal lesions could be produced with green streptococci as with B-hemolytic streptococci and to determine, by observation of such allergic phenomena as cutaneous hypersensitivity, secondary skin reaction and eye reaction, whether any of these factors might be associated with the greater incidence of glomerular lesions in sensitized animals.

In this connection one may recall here the work of Derick, Andrewes and Swift (6, 7, 8, 9), who showed that following the production of a local lesion in rabbits by intradermal injection of green streptococci there develops a generalized hyper-reactive or "hyperergic" state which is evidenced by increased skin reactivity, by a subsequent "secondary reaction" or spontaneous recrudescence of the local tissue reaction at the site of original injection, and by the development of an increased eye reactivity on corneal inoculation. Similar phenomena were described by Julianelle (10) with pneumococci. These authors were unable to demonstrate corresponding reactions following the injection of B-hemolytic streptococci and this was an additional reason for using green streptococci in the present experiments.

METHOD

Four strains of green streptococci were used, two of which (Thomas and Parsons) were obtained from the throats of patients with glomerular nephritis, and two (A-49 and V-110-A) from rheumatic fever patients. These latter were furnished through the kindness of Dr. Swift and Dr. McEwen of the Rockefeller Institute. The above strains were selected for their ability to produce well marked skin reactions after intradermal inoculation.

Altogether 57 rabbits were used in the experiments, 24 of which were normal and 33 "sensitized" by intra-cutaneous injections of living suspensions of green streptococci. The method of sensitization varied. In the earlier experiments doses representing 5 cc. of an 18-hour broth culture were injected at weekly intervals for four doses. In the remainder, smaller doses were used as in that way it was felt that greater degrees of hypersensitiveness might be obtained (11) and that the animals might be less liable to develop a partial state of immunity. Seven animals received weekly skin doses representing 1 cc. of culture; nine received doses of 0.5 cc. of culture and the remainder (13 rabbits) received first injections of 10^{-1}, 10^{-2} and 10^{-3} cc. of culture followed by a dose of 10^{-3} cc. for fourteen consecutive days. All cultures were grown in plain broth for 18 hours at 37.5°C. Measurements of the size of the skin lesions were recorded daily and any secondary reaction following the primary inoculation was noted. After the completion of the sensitizing inoculations, skin tests were made by injection of 10^{-3} and 10^{-4} cc. of culture and the eye sensitivity was tested by the method described by Derick and Swift (9). Both eyes after anaesthetization with procaine, were lightly scarified over one quadrant of the cornea with the point of an iridectomy knife, and a drop of centrifuged sediment from an 18-hour living broth culture was rubbed into the scarified cornea of one eye, the other eye being kept as a control. Daily observations were made for the development of conjunctival and corneal injection.

The technique of the actual injection into the renal artery was essentially similar to that employed in the experiments with B-haemolytic streptococci (1). Heavy bacterial vaccines were used, made by suspending in 3 cc. of saline the centrifuged sediment of either 25 or 50 cc. of an 18-hour plain broth culture. In each case the strain of organism used in sensitizing the animal was employed for the renal injection. In some of the earlier experiments living cultures were injected, but so many of the animals sickened and died that this method was discarded, and thereafter the vaccines were heated at 56°C. for 1 hour. Some of the strains, however, were not completely killed by this amount of heating, but the few viable organisms remaining apparently did not materially influence the results, for fully as marked lesions were observed with dead vaccine as when the

vaccines contained viable organisms. Injection was made directly into the left renal artery exposed through a laparotomy incision. The kidney itself was not handled in any way and the artery manipulated as little as possible. The right kidney was left intact as a control. Four days later the animals were killed and autopsied. Culture of the heart's blood was made by ventricular puncture immediately prior to autopsy.

RESULTS

Of the total number of animals used (57), lesions in the left kidney were observed in 19, or 33.3 per cent. That the lesion occurred more frequently in sensitized than in normal rabbits is shown by the inci-

TABLE 1

Comparison of incidence of glomerulitis in normal and sensitized rabbits

STRAIN	NORMAL				SENSITIZED			
	Total	0	+	Per cent	Total	0	+	Per cent
Thomas	10	10	0	0	20	14	6	30
A-49	2	2	0	0	3	3	0	0
V-110-A	5	4	1	20	5	1	4	80
Parsons	7	4	3	42.8	5	0	5	100
Total	24	20	4	16.6	33	18	15	45.4

dence of renal changes in the two groups. Four of the 24 normal rabbits (16.6 per cent) and 15 of the 33 sensitized animals (45.1 per cent) showed lesions in the left kidney (table 1). This difference, in common with that observed with the use of B-haemolytic streptococci where glomerulitis was obtained in 73.9 per cent of sensitized and 27.5 per cent of normal animals, indicates that previous sensitization is a predisposing though not an essential factor in the development of glomerular lesions.

In the sensitized animals no relation could be demonstrated between the occurrence of renal lesions and the presence of a hypersensitive or allergic state as shown by skin-test inoculation, by the occurrence of a secondary skin reaction following the first injection, or by the appearance of an eye reaction (table 2). By these tests, just as many hyper-

sensitive animals were observed among those that did not develop renal lesions as among those that did. The degree of hypersensitivity as shown by the extent of the reactions also appeared to be about equal in the two groups.

The readiness with which glomerular lesions were produced varied considerably with the strain of green streptococcus employed. Two strains (Parsons and V-110-A) appeared to be particularly well adapted for this purpose, as in sensitized animals lesions were produced in every case with the former and in all but one with the latter. This is in striking contrast with the results obtained with the other two strains. In experiments with one of these (A-49) no lesions were observed in the kidneys of any animals, while with the other (Thomas) less than half of the animals showed changes, usually of minor degree,

TABLE 2

Relation between skin reaction, secondary skin reaction and eye reaction to occurrence of renal lesions in sensitized animals

	SKIN REACTION		SECONDARY SKIN REACTION		EYE REACTION	
	+	0	+	0	+	0
	per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Renal lesion	93.6	6.7	53.3	46.7	66.6	33.4
No renal lesion	88.9	11.1	61.2	38.8	50	50

in the left kidney. The renal lesions produced by the Parsons and V-110-A strains also tended, as a rule, to be much more widespread and extensive than with the other strains. These variations depending upon the strain of organism used would appear to be of some significance, perhaps depending to some extent on heightened susceptibility on the part of the animals to these strains, an inference that is strengthened by the fact that both Parsons and V-110-A produced relatively large skin lesions at the first injection (table 4). A-49, however, also produced large initial lesions, though no renal changes resulted from its use.

DESCRIPTION OF RENAL LESIONS

The lesions observed were confined to the left kidney, the right or control kidney appearing normal in every case except for occasional

"spontaneous" focal mononuclear cell infiltrations or healed cortical scars which are sometimes observed in normal rabbits.

The kidneys which were the seat of the more marked histological changes often, though not invariably, exhibited distinctive gross characteristics. The left kidney in these cases was distinctly swollen and pale-yellowish in color with a pearly, semi-translucent lustre. No hemorrhages could be seen under the capsule. On cut section the cortex usually bulged from its capsule and was increased in thick-

TABLE 3

Degree of renal lesions produced in normal and sensitized animals

	NORMAL						SENSITIZED					
	0	+	++	+++	++++	Total	0	+	++	+++	++++	Total
Thomas	10	0	0	0	0	10	14	4	0	2	0	20
A-49	2	0	0	0	0	2	3	0	0	0	0	3
V-110-A	4	0	0	0	1	5	1	0	2	0	2	5
Parsons	4	0	1	1	1	7	0	0	0	3	2	5

TABLE 4

Average skin reactions at original injection

STRAIN	SUM OF TWO DIAMETERS (CM.)		
	10^{-1} cc.	10^{-2} cc.	10^{-3} cc.
Thomas	1.7	0.7	0.007
V-110-A	4.4	1.7	0.5
A-49	5.0	1.9	0.9
Parsons	6.6	1.9	0.6

ness. It was often very strikingly blanched and hence sharply demarcated from the underlying medulla which to all appearances was unaltered.

For the histological study, in addition to the ordinary haematoxylin-eosin stain, all sections were stained for the presence of bacteria and fibrin stains were made on a few selected cases. For the finer histology of the glomerular structure Heidenhain's modification of Mallory's anilin-blue stain as described by McGregor (12) was employed.

The lesions were designated according to degree and extent as

(+), (++), (+++), and (++++) and may briefly be summarized as follows:

(+) *Lesions.* Here the changes are practically confined to the glomeruli, there being no lesion in the tubular or interstitial tissues except in a few scattered regions where there is seen a zone of round-cell infiltration immediately surrounding a glomerulus. Lesions are observed in less than 25 per cent of the glomeruli, consisting for the most part of cellular proliferation both of the capillary endothelium and of the epithelium covering the glomerular tufts. In most cases the proliferation is confined to one glomerular tuft though occasionally the whole glomerulus is occupied by these cells, with compression of the basement membrane. Where present, this proliferative change is accompanied by a scattered exudate of polymorphonuclear leucocytes in and about the glomerulus. Sometimes a hyaline thrombus is observed in one of the glomerular loops. No bacteria are seen in any of these sections. The lesions are by no means diffuse and are rather of a focal nature.

(++) *Lesions.* About 50 per cent, or less, of the glomeruli in these sections show changes with proliferation of the large pale endothelial-like cells mentioned above as the most striking lesion. In these sections the proliferative process tends to involve the whole glomerulus rather than one tuft. Polymorphonuclear exudation in and about the glomeruli is more abundant and there are many small hyaline plugs in the glomeruli. In addition, scattered individual convoluted tubules connected with the altered glomeruli show flattening and degeneration of the lining epithelium. There is a noticeable perivascular exudate of small round cells in the deeper layers of the cortex. In one kidney from this series, small bacterial clumps are present in many of the glomeruli.

(+++) *Lesions.* Lesions are present in 50–75 per cent of the glomeruli. The striking change is the endothelial and epithelial cell proliferation in the glomerular loops, in these sections usually involving the whole glomerulus. The affected glomeruli are greatly swollen, filling the capsular space and compressing the capillary lumen. There is an extensive exudate of polymorphonuclear and mononuclear cells in the interstitial tissue adjacent to, as well as within, the glomeruli. Adhesions are commonly seen between the swollen glo-

merulus and its capsule. Capsular thickening is present in minor degree with a few crescent formations. In some of the sections there is extensive fusion and degeneration of the tubular epithelium; in others the evidences of tubular degeneration are very slight. In all cases, however, many of the tubules contain hyaline material and degenerating remains of red blood cells. Bacteria can be demonstrated in the glomeruli of only one animal. In these sections the lesion is well diffused throughout the whole cortical substance.

(++++) *Lesions.* These present the maximal lesions with only an occasional normal glomerulus remaining. There is extensive proliferation of glomerular endothelium and of the epithelial covering of the glomerular tufts as well as that lining the capsule so that the normal structure gives place to a solid mass of cells completely filling the capsular space and occluding the tuft capillaries which appear to be free of blood. Many large typical epithelial crescents are seen and because of the extensive glomerular swelling the capsular space is in most cases obliterated. There is a marked leucocytic exudation both in the glomeruli and diffused widely through the interstitial tissue. Bacteria can be demonstrated in all these sections, and in about half the cases are present in large numbers. They are distributed not only within the glomeruli but sometimes lie also within the lumen of the tubules. In the latter instance curious appearances may be produced from the intense and sharply demarcated leucocytic exudate surrounding the central mass of necrotic tubular remains in which bacteria are thickly seeded. This must obviously be a result of *in vivo* growth of organisms still viable after heating. Large deposits of fibrin containing degenerated red blood cells are present in the capsular space and between glomerular tufts. Many of the tubules as well contain serous or fibrinous material in which red cell shadows can be seen. There is extensive tubular change varying from cloudy swelling to complete disintegration and necrosis with desquamation of lining cells into the lumen. The whole process is so widespread and diffuse that hardly a normal glomerulus can be distinguished.

DISCUSSION

The dominant feature of the renal changes produced by this method appears to be a glomerulitis with tubular and interstitial changes of a

secondary nature. There is constantly present an extensive and characteristic proliferation of the glomerular epithelium and of the endothelium lining the glomerular capillaries to such a degree that the lumen in most cases appears to be completely obliterated. Leucocytic exudate is a well-marked feature in the glomerulus and capsular space as well as (in the more marked lesions) in the interstitial tissue of the cortex. Degeneration of the tubular epithelium accompanies or follows the glomerular damage and may be secondary to it. It is noteworthy that in the kidneys showing most damage bacterial clumps are frequently seen in the glomerular capillaries after 4 days, while in the normal and only slightly altered kidneys the bacteria, even when very heavy suspensions are injected, disappear entirely. In fact, in a few animals which died within a few minutes after injection (apparently from ether intoxication) surprisingly few bacteria could be seen in the injected kidney.

The inflammatory picture, as far as the glomeruli are concerned, impresses one as being of an exudative and proliferative nature in about equal degree, with added degenerative tubular changes in the more marked cases. In many respects the histological picture resembles some of the features of glomerular nephritis in man though the inflammatory nature of the process is here much more impressive. That such is the case is not surprising, since the severity of the renal injury in these experiments, with consequent rapid development and progress of the lesion, may be expected to introduce factors which are absent in human nephritis.

The proliferative feature is much more marked than in the experiments of similar nature performed with B-haemolytic streptococcus. One can be quite certain that the changes here described have nothing in common with the so-called "spontaneous nephritis" of rabbits, as in no case were the above lesions observed in the right or control kidney. Nor does it seem possible that they can be attributed to thrombotic action, for in the cases in which scattered infarctions occurred from thrombosis of smaller arteries the picture in the infarcted areas is quite different and consists of cytolytic necrosis with a well demarcated heavy marginal zone of leucocytes.

The greater frequency of renal lesions in the sensitized group in these experiments, as in those performed with B-haemolytic streptococci,

raises some interesting but as yet unsettled questions. On the one hand, one may assume that the process of sensitization has caused a definite alteration in tissue reactivity by which the inflammatory response becomes intensified; in other words that a true allergic state has arisen. That lesions did occur in some of the normal unsensitized animals might be attributed to a natural or inherent susceptibility to the green streptococcus and in fact many animals did exhibit marked skin reactions at the first test injection before any sensitization had been attempted.

Another and highly probable explanation, however, need assume no allergic reaction. From the persistence of bacteria in the kidneys which showed the more marked lesions one might suppose that the development of renal lesions depends on intimate and more or less prolonged contact of the streptococcal bodies with the glomeruli. It may then be that in "sensitized" animals the injected suspension is more readily agglutinated than in normal animals and the resulting clumps would be arrested in the glomeruli more readily than a fine suspension. The fineness of the suspension used in these experiments was not determined and it is possible that in the normal animals that developed renal lesions the vaccines contained coarser particles. Certainly in these animals the lesions were fully as florid and well-marked as in the sensitized rabbits, contrary to what one would expect were an altered tissue reactivity or allergic state the sole responsible factor. A positive conclusion on this point, however, cannot be postulated from the results of these experiments as performed, and further investigations taking into account the fineness of the bacterial suspension are necessary. Whatever the mechanism involved, there appears to be something in the process of artificial sensitization which renders the kidney of the experimental animal more susceptible to injury by the streptococcus.

CONCLUSIONS

By the use of certain strains of green streptococcus one may produce in rabbits glomerular, tubular and interstitial changes which simulate in some respects the glomerular or hemorrhagic nephritis of man.

Different strains of green streptococci differ very markedly in their power to produce these renal lesions.

The lesions produced are even more extensive than those previously obtained with B-haemolytic streptococcus.

In general, lesions were found somewhat more frequently in sensitized than in normal animals, though within the former group the degree of allergy as estimated by skin and eye reactivity apparently bears no relation to the development of renal lesions.

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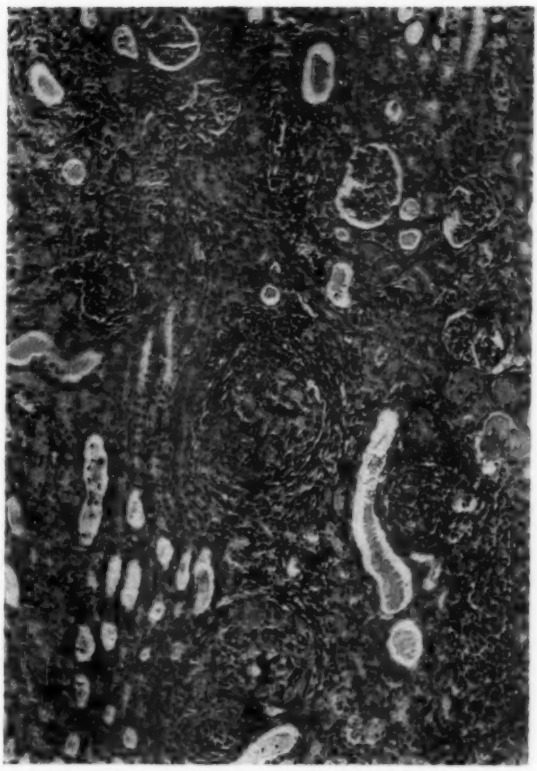

FIG. 1. Rabbit 563. Sensitized to V-110-A Streptococcus. 3 cc. vaccine injected into left renal artery. Animal killed 4 days after injection Low-power view of left kidney; note two enormously enlarged glomeruli filled with proliferated cells and fibrin. Diffuse cellular exudate. Hyaline and fibrinous material in many tubules.

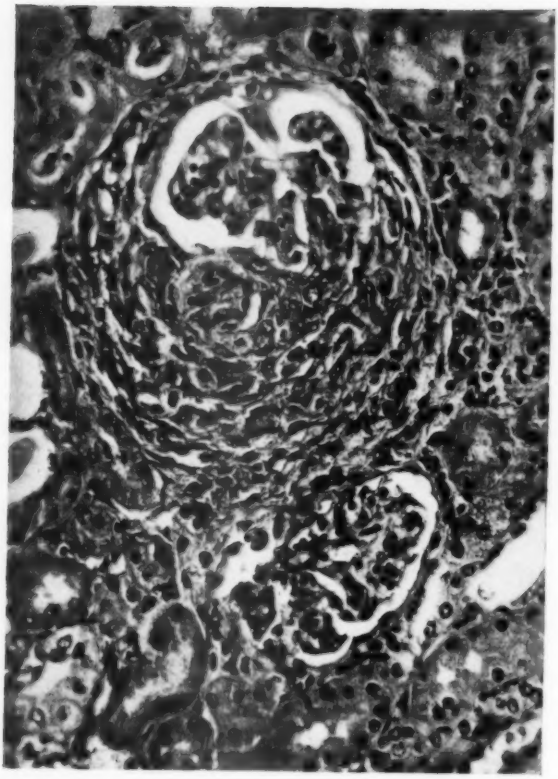

FIG. 2. Same as Fig. 1. High-power view of glomerulus showing large crescent formation.

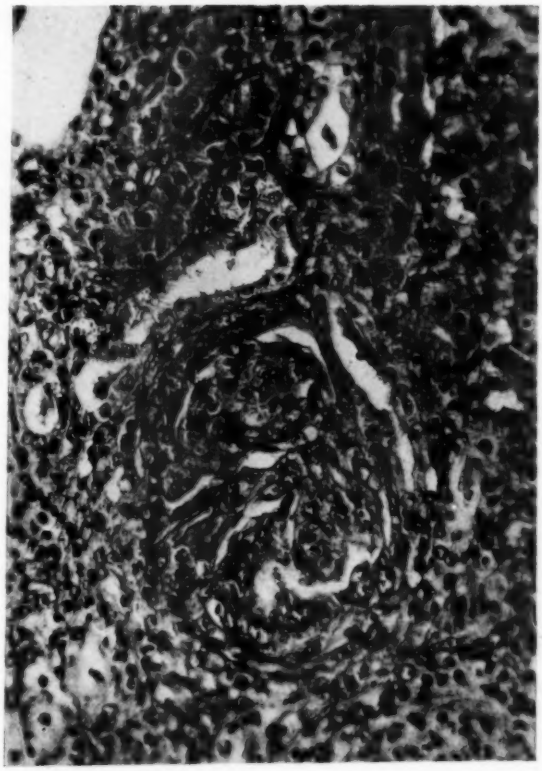

FIG. 3. Same as Fig. 1. High power of glomerulus showing proliferation of endothelial and epithelial cells, capsular thickening and adhesion to capsule.

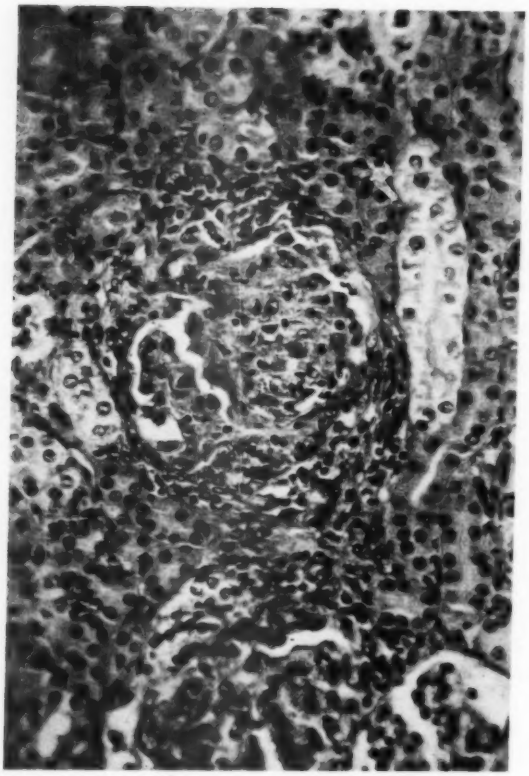

FIG. 4. Rabbit 562. Sensitized to V-110-A Streptococcus. 3 cc. vaccine injected into left renal artery. Animal killed 4 days after injection. High-power from left kidney; glomerulus with cell proliferation, capsular adhesions, polymorphonuclear exudate.

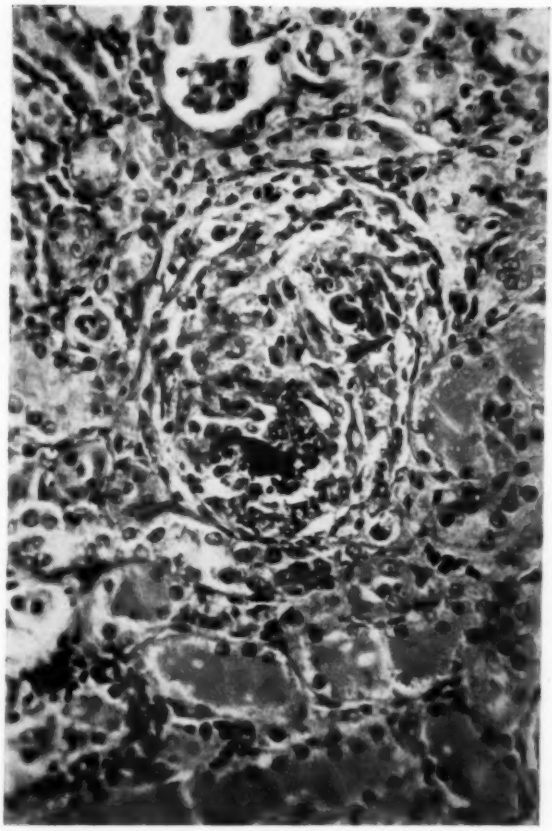

FIG. 5. Same as fig. 4. High-power glomerulus showing two masses of fibrin enclosing bacteria. Cellular proliferation and exudate of polymorphonuclears. Adjacent tubule filled with hyaline material.

FIG. 6. Rabbit 580. Sensitized to Parsons Streptococcus. 3 cc. vaccine injected into left renal artery. Animal killed 4 days after injection. Low power; diffuse cellular exudate. Swollen glomeruli with cellular proliferation. Tubular degeneration.

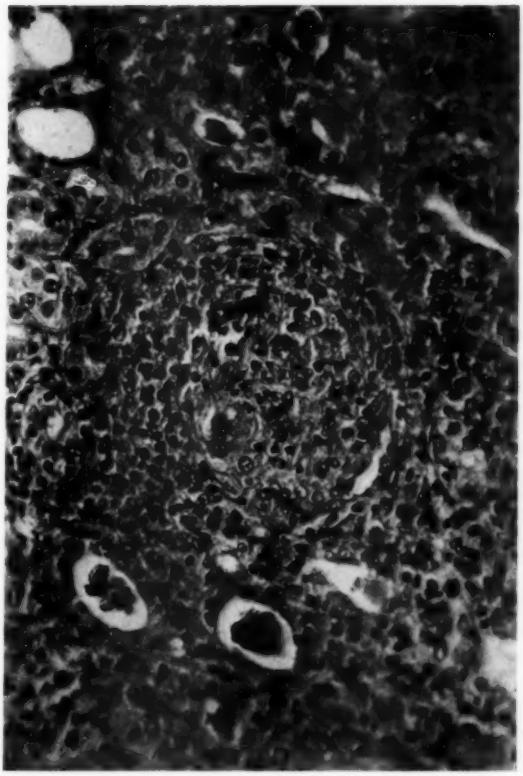

FIG. 7. Rabbit 551. Normal unsensitized animal. 3 cc. of Parsons Streptococcus injected into left renal artery. Animal killed 6 days after injection. High power, adherent thickened glomerulus. Extensive exudate of mononuclear and polymorphonuclear cells in and about glomerulus.

INTRAVENOUS UROGRAPHY IN CHILDREN

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The particular value of intravenous urography in children has already been emphasized by several authors, and many papers have been contributed to show the advantages or limitations of retrograde versus intravenous urography. Undoubtedly there are cases in which one method is superior to the other, but most workers are now agreed that the scope of usefulness of the intravenous method generally exceeds that of the retrograde. This is particularly true for infants and children in whom the difficulties of cystoscopy are obvious.

Despite the large number of articles on the subject, however, very few authors have attempted a comparison of the results obtained by the intravenous and the retrograde methods. Herbst (1) (2) and Ravasini (3) have compared the two groups in a general way and listed the types of cases in which each should prove superior. They did not, however, compare results by both methods on the same patients. To the present time the work of Lanman and Mahoney (4) (5) is the only contribution which gives the findings by each method in the same cases.

Our own series includes 56 consecutive patients whose symptoms directed attention to the urinary tract. In each instance the urinary system was investigated by the intravenous injection of Iopax. Through the kindness of members of the gynecological staff, retrograde pyelograms were also obtained on ten of these patients. The comparative results will be discussed later.

METHOD

Iopax was used for the intravenous urograms. Our technique differed only slightly from the usual procedure as outlined in the manufacturer's directions. Injections were usually made during the early afternoon. For children over two years of age there was no preliminary preparation but in infants gas in the intestine was such a consistently

complicating factor that pituitrin was administered intramuscularly one-half hour before the injection of the Iopax and the abdomen massaged for ten minutes with a rectal tube in place. X-ray films of the abdomen, taken before and after the administration of the pituitrin have demonstrated its usefulness. Enemata, on the other hand, increase the amount of intestinal gas, while the administration of a mild cathartic, such as compound licorice powder, seems to have no effect.

The 30-per-cent Iopax solution was injected over a period of 5 to 10 minutes into any available vein. Good visualization was obtained more consistently when the dose for infants and children was made proportionately larger than for adults. For this reason, 3.3 cc. of 30-per-cent solution per kilo of body-weight was injected; in no case was less than 20 cc. or more than 60 cc. administered. This is approximately three times the adult dose per kilo, but its rationale seems obvious. Theoretically, at least, if the lumen of a child's ureter is roughly one-third the diameter of the adult ureter, three times the concentration of iodine will be necessary to give the same x-ray opacity. No toxic symptoms are observed with this dosage; in fact, many times this amount (10 cc. per kilo) has been given by Lanman and Mahoney (5) without harmful results. Moreover, Heckenbach (6), Viethen (7) and Rosenbush (8) have independently adopted this increased dosage for children, and the directions accompanying the latest preparations of Iopax now call for similar doses.

X-ray films were taken 15, 45 and 90 minutes after the beginning of the injection. All exposures were made with the child lying on his back; wherever possible the Buckey diaphragm was used. The compression band was helpful in increasing the amount of iodine in the kidney pelvis but it so compressed the ureters that its use was abandoned wherever ureteral outline was also desired.

A majority of the older children complained of an uncomfortable feeling of warmth and thirst at the time of the injection; in a few there was obvious flushing with increase in pulse rate but in none was there any untoward reaction and the initial discomfort usually lasted but a few minutes. Water was not allowed until after the 45-minute film had been taken and an attempt was made to have the child void only after this exposure.

RESULTS

The results obtained varied over a wide range from excellent visualization of the urinary tract to no apparent excretion of the dye. In analyzing these results the films were divided into three groups (1) Excellent, (2) Satisfactory for Interpretation and (3) Unsatisfactory. Those in the first group showed good definition of the entire urinary tract; those remaining were classed as satisfactory for interpretation if one could diagnose or exclude any abnormality by a study of all three exposures. The remainder were called unsatisfactory. In Table I is listed the distribution in these three groups. Excellent results were obtained in 40 per cent; an additional 20 per cent were readable, making a total of 60 per cent satisfactory results and 40 per cent unsatisfactory.

TABLE I

Analysis of results

PATIENTS	NUMBER	SATISFACTORY		UNSATISFACTORY
		Excellent	Readable	
Under two years of age	14	2	3	9
		5		
		35%		65%
Over two years of age	42	20	8	14
		28		
		65%		35%
Total	56	22	11	23
		33		
		60%		40%

It was always difficult to obtain good results in infants under two years of age. This was due to the fact that children of this size cannot be made to lie still long enough to permit adequate x-ray exposure, to the persistence of gas in the intestine and probably also to the small lumen of the ureter. If these results are, therefore, rearranged in age groups above and below 2 years, it will be seen that only 35 per cent of the films taken on infants were satisfactory, compared with 65 per cent of those on older children (Table I). It must be remembered, however,

that these figures are derived by a consideration of all attempts made. No film was excluded because the patient moved, for faulty exposure or

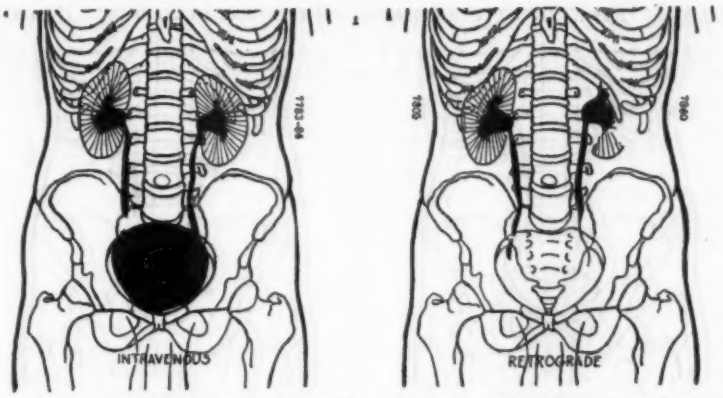

FIG. 1. Case 1. Five-year-old female. Pyelitis. Dilated ureters and renal pelvis.

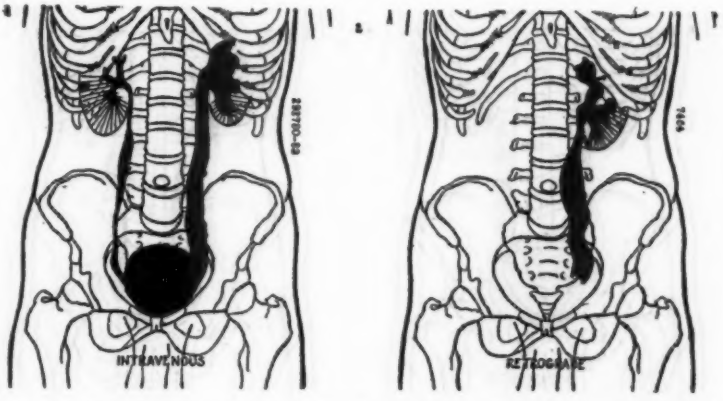

FIG. 2. Case 2. Eleven-year-old female. Pyelitis. Dilated ureters and renal pelvis, especially left.

any other extraneous reason. Therefore, the figures represent a fair estimate of the results which may be obtained under average conditions.

In ten of the patients, in whom some anatomical abnormality was

demonstrated by the x-ray findings, cystoscopic examinations were made and retrograde urograms obtained. In the accompanying figures (figs. 1 to 10) are compared the results in each case by both

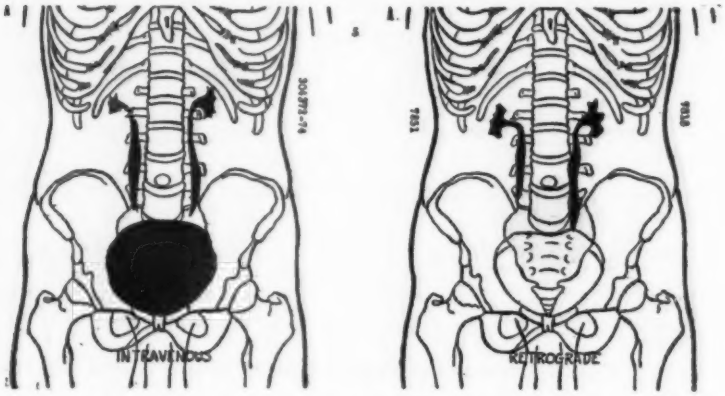

FIG. 3. Case 3. Two-year-old female. Pyelitis. Slightly dilated ureters

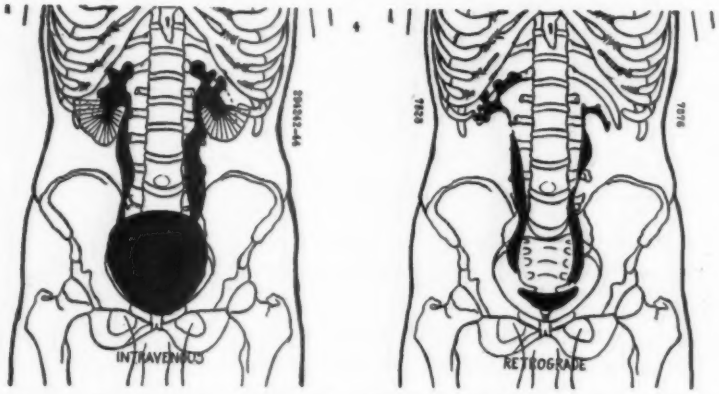

FIG. 4. Case 4. Seven-year female. Pyelitis. Dilated ureters and kidney pelvis.

the retrograde and intravenous method. This mode of illustration was adopted because the photographic contrast in films taken after Iopax injection is almost never sufficient to allow satisfactory reproduction.

Furthermore, the urinary tract must always be visualized by a mental composite of the three films taken at 15, 45 and 90 minute intervals.

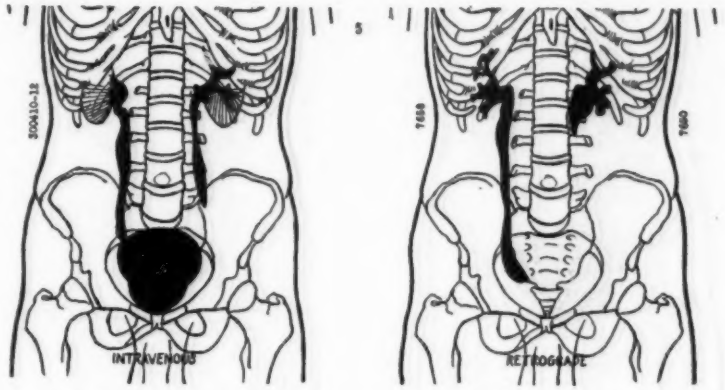

FIG. 5. Case 5. Two-year female. Pyelitis. Dilated ureters and kidney pelvis.

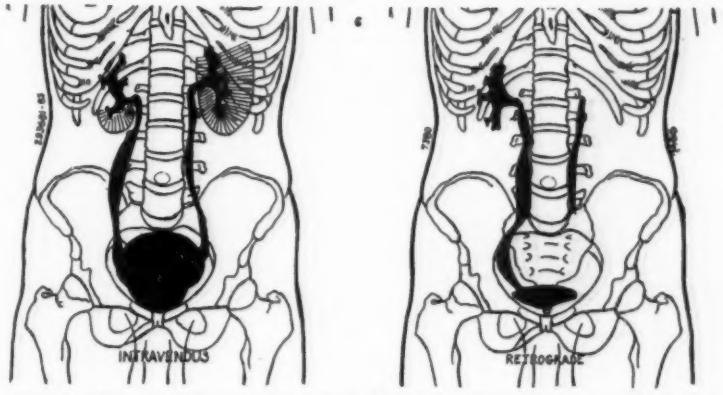

FIG. 6. Case 6. Five-year female. Pyelitis. Dilated ureters and kidney pelvis.

The drawings of the retrograde urograms were obtained in each instance from two films, one from each side, taken at two different cystoscopic examinations.

All of the patients had pyuria. In seven this condition was attributed to pyelo-ureteritis; all of these patients showed dilated ureters

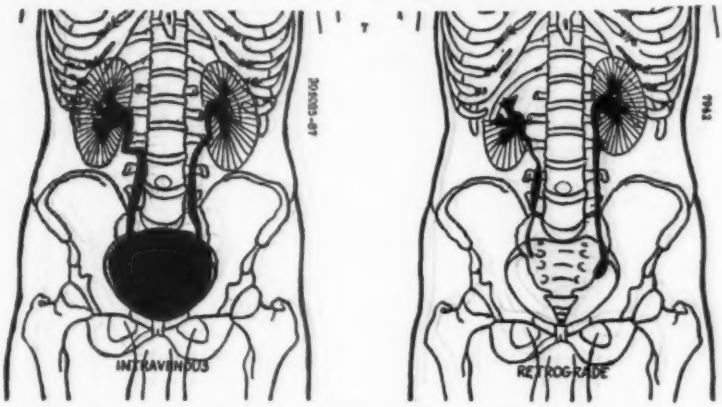

FIG. 7. Case 7. Three-year female. Pyelitis. Slightly dilated ureters

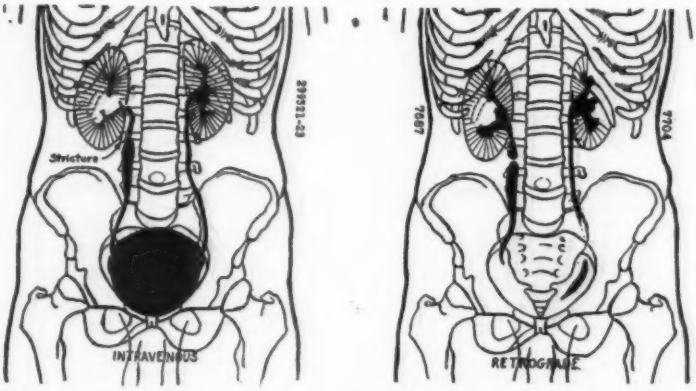

FIG. 8. Case 8. Five-year female. Kidney abscess; stricture of ureter; dilated ureter. The abscess in the right kidney is located by the absence of any Iopax in that region.

of various degrees. One patient was found to have multiple kidney abscesses with a stricture of the ureter. In another a diagnosis was made of congenital absence of the right kidney, congenital urethral

valve and associated hydronephrosis and hydro-ureter on the left. In case 10 the condition was diagnosed as megalo-ureter.

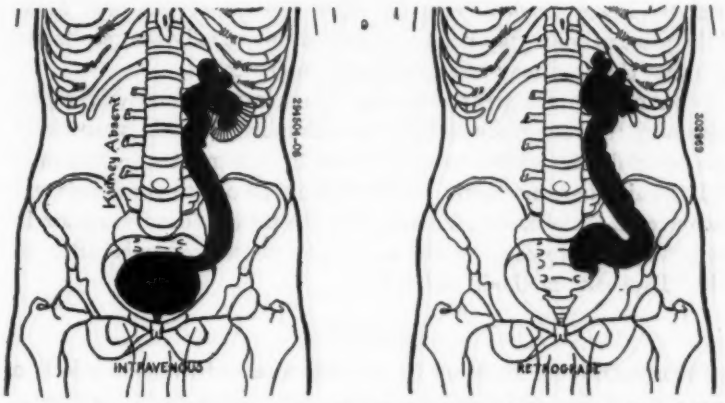

FIG. 9. Case 9. Fifteen-months male. Congenital urethral valve. Congenital absence of right kidney. Dilated ureter and kidney pelvis.

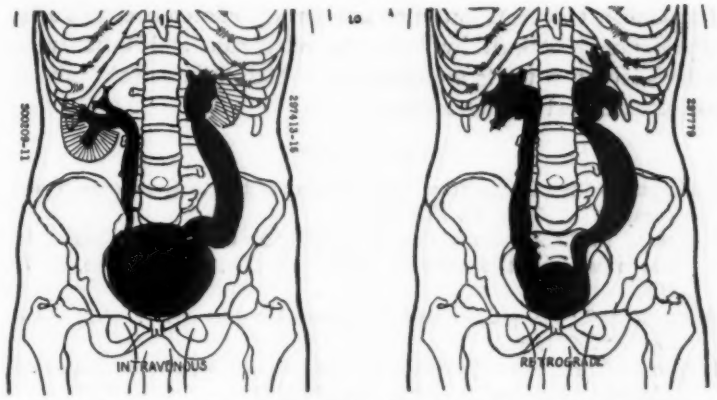

FIG. 10. Case 10. Four-year female. Megaloureter. Dilated ureters and kidney pelvis.

It can be seen from the figures that in all of the cases the results obtained by the retrograde and intravenous methods are practically identical. In no instance was a diagnosis made by one method that

could not have been derived independently by the other. The results obtained by either route are not always satisfactory at the first attempt. Similarly, in any single attempt by either method, certain small areas of the urinary tract may not be visualized but usually the results are such that the films may be satisfactorily interpreted.

In our opinion, the great advantage which intravenous pyelography holds over the retrograde method is its simplicity. This is especially true for children, where cystoscopy can be accomplished often only with the aid of an anesthetic. Several times an obscure diagnosis was uncovered by information derived from the intravenous pyelogram in cases where cystoscopy would have been considered only after all other diagnostic methods had failed.

SUMMARY

Pyelograms were made on 56 children after intravenous injection of Iopax. A dose of 3.3 cc. of a 30-per-cent solution per kilo of body-weight was found satisfactory. This is approximately three times the adult dose per kilo. Good results were obtained in only 35 per cent of infants under two years but in 65 per cent of children over this age.

Pyelograms obtained by both the retrograde and intravenous methods on ten patients are compared. The outlines of the urinary tract are identical by each method.

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THE SPECTROGRAPHIC DETECTION OF LEAD IN THE BLOOD AS AN AID TO THE CLINICAL DIAGNOSIS OF PLUMBISM[1]

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The diagnosis of saturnism in children is usually made on the basis of the results of clinical investigation, since the labor of collecting excreta and the difficulties presented by their chemical examination are such that these procedures are undertaken infrequently, even in institutions.

During the course of an epidemic of poisoning by lead in Baltimore, it became desirable to have at hand a reliable procedure by means of which a specific diagnosis of plumbism could be made rapidly and without great technical difficulties, especially with a view to detecting "leaded" individuals without clinical manifestations of disease.

Since it is known that lead is transported in the circulating blood, it seemed possible that it might be present in the blood of our patients in amounts sufficiently great to be detectable by spectrographic analysis. This we found to be the case in the samples of blood from patients with lead poisoning which we have so far examined.

The technique which we have used to study the blood spectrographically is as follows. Five cubic centimeters of blood are withdrawn from a vein into glassware which has been cleaned by washing it in strong nitric acid and rinsing in distilled water. Two cubic centimeters of strong distilled sulphuric acid are added to the blood in a silica ashing dish and the whole is charred over an open flame. Ashing is completed in twelve to twenty-four hours in an electric muffle furnace at a temperature not exceeding 500°C. The resultant ash is powdered and triturated in an agate mortar and is then ready to be examined spectrographically.

[1] Submitted for publication, September 24, 1932.

The ash is burned in an electric arc between graphite electrodes. The light is concentrated by a condensing lens and focused on the slit of a Hilger E_1 spectrograph. The spectrum is recorded on a photographic plate and the *raies ultimes* of lead are sought by direct comparison with the spectrum of a known lead compound photographed directly beneath that of the ash.

By this method we have succeeded in demonstrating appreciable quantities of lead in the blood of nine children who were suffering

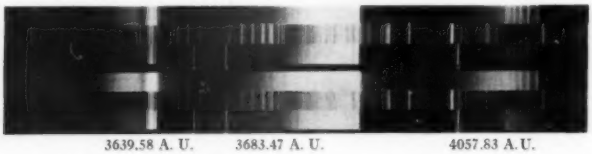

FIG. 1. The figure shows two spectrograms for comparison, one from the blood of a normal child, the other from the blood of a child with encephalo-myelitis resulting from lead poisoning. Triplet A is the normal spectrogram; Triplet B, that of a child with plumbism. In the triplets the upper bar is the control spectrum of the empty graphite electrodes; the middle bar, the spectrum of the ash under examination; and the lower bar, the spectrum of a known solution of lead nitrate. The significant lines are marked by white dots. It will be seen on examination that the spectrum of the blood of the poisoned child shows the lead lines very distinctly. In the normal blood only one of these lines is even faintly visible.

from various manifestations of plumbism. The blood of six normal children used as controls either gave negative results or showed questionable evidence of traces.

It would appear even from this small series of cases that the spectrographic examination of the blood permits an exact diagnosis of lead poisoning within twenty-four hours after the blood is withdrawn from the vein of the patient.

FAILURE TO INDUCE OVULATION IN THE RABBIT BY BLOOD TRANSFUSION FROM THE PREGNANT DOE

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The increasing importance of the rabbit as a test animal for the study of the sexual hormones seems to justify any experimental research leading to a better knowledge of the biology of reproduction in this rodent.

The search for a gonad-stimulating hormone in the urine of the pregnant doe has given negative results to Zondek (1), to Snyder and Wislocki (2) and to Schlotthauer and Magath (3).

As far as the author knows, no research has been published concerning the possible effect of blood transfusion from the pregnant to the non-pregnant rabbit in order to see if it produces ovulation.

Since the work of Friedman (4) we know that the intravenous injection of a rather small amount of urine of pregnant women causes ovulation and luteinization in the ovary of the mature rabbit. Snyder and Wislocki (5) using a concentrated extract of urine of pregnant women (Parke, Davis & Co.) which, in several cases produced ovulation when injected at a dose of 0.1 cc. into the veins of the adult rabbit, found that the active principle was not present in the urine of the injected animal in sufficient amount to induce ovulation in another rabbit, unless a dose of 20 cc.—approximately 200 times the usual ovulation dose—was injected intravenously into the first animal.

Such results suggest the idea that the kidney of the rabbit has a rather high threshold as regards the elimination of this ovulation substance. If that hormone is normally present in the pregnant rabbit's blood, it may be that it is not eliminated in sufficient amount to induce ovulation when the urine of a pregnant rabbit is injected into a normal mature doe.

[1] Fellow of the John S. Guggenheim Memorial Foundation, from the Department of Gynecology, University of Chile, Santiago, Chile.

In the present work the author has tried to detect the presence of a gonad-stimulating hormone in the blood of the pregnant doe by means of small and large blood transfusions from the pregnant to the normal adult animal. In this way the possible action of the kidney is eliminated.

METHODS

Mature, healthy does, 15 to 19 days pregnant, were used as donors. As recipients we used adult, isolated rabbits which had demonstrated in a previous test made with 5 cc. of urine of pregnant women that they were quite sensitive to the gonad-stimulating hormone contained in it.

The four recipient animals had been isolated in individual cages for periods of not less than a month.

In the two cases in which large transfusions were performed, the blood volume was calculated as indicated by the formula of Dreyer and Ray (6).

TECHNIQUE

As Zondek (1) has demonstrated, sodium citrate does not destroy the gonad-stimulating hormone of the blood of pregnant women. For this reason we used this substance to avoid coagulation.

In spite of the fact that no blood groups have been yet demonstrated in the rabbit, we made previously to each one of the transfusions a direct matching of the blood of both animals, in order to be sure of a perfect compatibility.

The smaller transfusions were performed with a common syringe containing 1 cc. of 1 per cent sodium citrate per 5 cc. of blood. The blood was removed from the jugular vein of the donor.

For making the larger transfusions the blood was aspirated into a flask containing 5 cc. of a 2 per cent sodium-citrate solution and then injected into the jugular vein of the recipient with the Jube transfusion apparatus.

The recipient animals were explored 18 hours after the transfusion to see if ovulation was or was not present. As criteria for recognizing the ovulation we have followed the signs described by Wilson and Corner (7).

RESULTS

All the transfused animals survived. Both donor rabbits from which a large amount of blood was removed died soon after the operation.

The amount of blood transfused, further data and the results obtained are shown in table 1.

The percentage of blood injected in relation to the blood volume of the transfused animals shows that in the recipient does B15 and B22 a

TABLE 1

The effect of blood transfused from the pregnant to the non-pregnant rabbit

	NUMBER OF RABBIT AND DAYS OF PREGNANCY	WEIGHT OF RABBIT	BLOOD VOLUME CALCULATED	AMOUNT OF BLOOD REMOVED	AMOUNT OF BLOOD INJECTED	PER CENT OF BLOOD TRANSFUSED IN RELATION TO BLOOD VOLUME OF RECIPIENT	PER CENT OF BLOOD REMOVED FROM DONOR	OVULATION
		grams	*cc.*	*cc.*	*cc.*			
Exp. 1	B3. Donor, 15 days	3,025		10				Negative
	B96. Recipient	2,370			10			
Exp. 2	B3. Donor, 15 days	3,025		10				Negative
	B98. Recipient	2,410			10			
Exp. 3	B11. Donor, 17 days	4,079	161	62.5			38.8	Negative
	B15. Recipient	3,510	146	50	62.5	42.8		
Exp. 4	B16. Donor, 19 days	2,430	114	45.5			39.9	Negative
	B22. Recipient	2,980	131	40	45.5	34.7		

volume of blood was injected amounting respectively to 42.8 per cent and 34.7 per cent of their own blood and to 38.8 per cent and 39.9 per cent of the total blood volume of the pregnant donors.

In spite of such a high proportion of blood injected the ovulation failed to occur.

These results seem to show that in the blood of the pregnant rabbit a principle inducing ovulation in the adult normal doe does not exist or is present in extremely small amounts.

SUMMARY

Adult female rabbits isolated for a period of no less than a month were transfused with from 10 to 62.5 cc. of blood from pregnant does.

In spite of the fact that the amount injected represented in two cases 38.8 per cent and 39.9 per cent, respectively, of the total amount of blood calculated as existent in the pregnant donors, ovulation did not occur, a fact which was determined by laporotomy performed 18 hours after the transfusion.

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BOOK REVIEWS

Imhotep to Harvey. Backgrounds of Medical History. By CHARLES N. B. CAMAC, M.D. 324 Pp. $3.75. (*Paul B. Hoeber, Inc., N. Y., 1931.*)

This book gives a rapid survey of the background of medicine. The author starts with a brief chapter on the evolution of the scientific method and traces in the succeeding chapters the development of medicine from the earliest records to the period of the Renaissance.

The book is written for student reading. Each chapter is prefaced with an outline of the scientific pursuits, medical practices, records and teachers of that particular period under discussion. Questions that may occur to every medical student as to the origin of the symbols used in prescriptions, the use of the serpent as an emblem in medicine, the etymology of medical terms, are answered in this text. The author not only gives a record of medical development, but also traces the effect of the general development of history on medicine, how the influence of Christianity, the capture of Constantinople by the Turks, the development of the physical sciences played a part in molding and changing the character of medical progress.

The last chapter is especially valuable. The author includes a group of interesting quotations from original sources and a list of readable book and journal references for collateral reading.

C. L. G.

Selected Writings of John Hughlings Jackson. Edited by James Taylor, for the Guarantors of Brain, with the Advice and Assistance of Gordon Holmes and F. M. R. Walshe. Volume I, Epilepsy and Epileptiform Convulsions. Volume II, Evolution and Dissolution of the Nervous System, Speech, Various Papers, Addresses and Lectures. 500 Pp. (*Hodder & Stoughton, London, 1931 and 1932.*)

Hughlings Jackson was the great prophet of modern clinical neurology in England. Working just at the beginning of the investigative and experimental period, he outlined and defined the essential problems and awakened a healthy curiosity among doctors dealing with patients. His papers are difficult to read, for the style is labored and obscure. Before entering medical school he had the equivalent of a poor grammar school education. Moreover, in spirit, Jackson was primarily a philosopher and his writings are touched with mysticism. His personality and life are as interesting as his neurological work. Jackson was occupied particularly with abnormalities of the cerebral cortex, hemiplegia, epilepsy, aphasia and migraine. Perhaps his greatest contribution to neurology was the sub-division of physical findings after a cerebral lesion into those dependent on

loss of nerve substance, release from normal control of lower centers and irritative phenomena.

The first volume contains a selection of papers upon epilepsy written from 1861 to 1911. There is a vast amount of repetition. He pointed out the essential features of convulsions and realized that they were due to sudden and violent discharges from localized areas of gray matter. The attacks dependent on lesions of the motor cerebral cortex were subjected to particular study, inasmuch as they are simpler, slower in their progress and easier to analyze than generalized fits. This type of attack is now commonly known by his name.

The second volume is devoted to papers upon a multitude of subjects. Living as he did in the days of Herbert Spencer and at a time when the theory of evolution was discussed by all thinking people, it is not strange that he should have tested this new thesis in his particular field. Jackson's papers upon aphasia are based upon careful and sane observations, and are of as much interest today as when they were written. He avoided the mistake of the French writers who endeavored to subdivide cases into distinct groups, each dependent on circumscribed lesions in the cortex. Jackson was the first to urge the use of the ophthalmoscope in the neurological examination. His observations upon cerebral neoplasms, startling as they were at the time, seem commonplace to us now.

The soundness of Jackson's theories makes them still of vital interest, although more than twenty years have elapsed since the death of the author. These two volumes, the compilation of his grateful pupils, should be in every neurological library.

O. R. L.

Applied Physiology. By SAMPSON WRIGHT. 4th Edition. 22°. 552 Pp. $5.50. (*Oxford Univ. Press, 1931.*)

Much new material, especially in the field of internal secretions, has been added to this edition. The book continues to hold its own as an up-to-date text for those inclined to review the applications of physiology to the practice of medicine, and for students wishing a text to supplement the general study of physiology.

C. L. G.